

Safety and activity of R07300490, a bispecific CD40 agonist targeted to fibroblast activation protein, in patients with advanced solid tumors: a single-arm, multicenter, first-in-human, phase 1 trial

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PROTOCOL

TITLE: AN OPEN-LABEL, MULTICENTER, DOSE-ESCALATION AND EXPANSION, PHASE I STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, AND ANTI-TUMOR ACTIVITY OF RO7300490, A FIBROBLAST ACTIVATION PROTEIN- α (FAP) TARGETED CD40 AGONIST, AS SINGLE AGENT OR IN COMBINATION WITH ATEZOLIZUMAB IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS

PROTOCOL NUMBER: WP42627

VERSION: 3

EUDRACT NUMBER: 2020-004489-21

IND NUMBER: To be determined

TEST PRODUCT: RO7300490, atezolizumab, tocilizumab

SPONSOR: F. Hoffmann-La Roche Ltd

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FINAL PROTOCOL APPROVAL

Date and Time (UTC)
26-Jan-2022 11:08:01

Title
Company Signatory

Approver's Name

[REDACTED]

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RO7300490—F. Hoffmann-La Roche Ltd
Protocol WP42627, Version 3

PROTOCOL ACCEPTANCE FORM

TITLE: AN OPEN-LABEL, MULTICENTER, DOSE-ESCALATION AND EXPANSION, PHASE I STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, AND ANTI-TUMOR ACTIVITY OF RO7300490, A FIBROBLAST ACTIVATION PROTEIN- α (FAP) TARGETED CD40 AGONIST, AS SINGLE AGENT OR IN COMBINATION WITH ATEZOLIZUMAB IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL AMENDMENT, VERSION 3 RATIONALE

Protocol WP42627 version 2 was amended to further ensure the overall safety of study participants, including an update of the safety management guidelines for the IMP atezolizumab, in alignment with atezolizumab Investigator's Brochure; and the application of a more stringent trigger for the laboratory analysis of Immunoglobulin E (IgE)-mediated hypersensitivity reaction. The list of tumor indications for study enrollment has also been limited to 10 indications to increase the confidence in study results relevance. In addition to these substantial changes, further clarifications were introduced. All changes to the protocol, along with the rationale for each change are summarized below.

Section 1.3 (Schedule of Assessments): The SoA Tables 1 and 3 have been updated to specify that:

- IgE/tryptase analysis has to be performed in case of hypersensitivity reaction Grade 2 and higher (previously: \geq Grade 3). This change is reflected by a corresponding update in protocol Appendix 4, Table 1.
- CT or MRI of the head is mandatory at screening (previously: optional). This change is reflected by a corresponding update in Section 8.1.1.

Section 2.3 (Benefit/Risk Assessment): The benefit/risk evaluation derived from the emergent study data was included and the language about COVID 19 benefit/risk was updated to align with the most up-to-date Sponsor evaluation and recommendations.

Section 5.1 (Inclusion Criteria): Criterion #5 was rephrased and all references to the Medical Monitor were removed to comply with the Sponsor's GCP Council Statement "Medical Monitor Advising of Protocol Specific Criteria" and reflect that the enrollment of a participant in the study is the sole responsibility of the Investigator. In addition, the list of tumor indications for study enrollment has been revised and limited to 10 indications to increase the scientific relevance of the study results.

Section 5.2 (Exclusion Criteria): Criteria #3, #10 and #22 were rephrased and all references to the Medical Monitor were removed to comply with the Sponsor's GCP Council Statement "Medical Monitor Advising of Protocol Specific Criteria" and reflect that the enrollment of a participant in the study is the sole responsibility of the Investigator. Criteria #1 and #5 were updated to reinforce participant safety (e.g., a CT or MRI scan of the head at screening is made mandatory). Criterion #12 was rephrased to clarify that both, a hepatitis B surface antigen (HBsAg) and a total hepatitis B core antibody (HBcAb) test are required.

Section 6.1.1 (RO7300490 Administration): Guidance about the infusion times and post-infusion observation times for participants who dose-escalate while on study or when

transferring from the imaging sub-study have been specified in order to ensure participant's safety.

Section 6.1.4 (Pre-medication for Participants Receiving RO7300490): Cytokine Release Syndrome (CRS) reporting requirements have been updated to align with the definition of CRS as per ASTCT, which are presented in protocol Section 8.3.9.1, Table 13, and in Appendix 9.

Section 6.5.2 (Prohibited Therapy): It was clarified that up to 48 hours of treatment with corticosteroids as premedication is allowed during the study for participants with contrast allergy.

Appendix 2 (Adverse Events: Definitions and Procedures for Evaluating, Follow up and Reporting): it was clarified that the assessment of severity for CRS uses the ASTCT Cytokine Release Syndrome Consensus Grading (under Section 3.1).

Appendix 5 (Contraceptive Guidance and Collection of Pregnancy Information): The section was updated to comply with the most recent Sponsor guidance on Good Pharmacovigilance practice. It was specified that the Sponsor will collect infant health information if a female participant becomes pregnant, upon her consent. For this purpose, a new Infant Authorization Form is introduced.

Appendix 10 (Management Guidelines for Immune-Mediated Adverse Events Associated with RO7300490 and/or Combination Therapy with RO7300490 and Atezolizumab): Management guidelines have been revised based on atezolizumab Investigator's Brochure to reflect the most up-to-date atezolizumab safety information.

Additional minor changes have been made to improve clarity and consistency of the protocol. Substantial new information appears in Book Antiqua italics. The synopsis has been updated to reflect these changes. 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
ANA	Anti-nuclear antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen-presenting cell
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	Area under the curve
BML	Below measurable limit
C1D1	Cycle 1 Day 1
cANCA	Circulating anti-neutrophil cytoplasmic antibody
CD40L	CD40 ligand
CIT	Cancer immunotherapy
CL	Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
cMRI	Cardiac magnetic resonance imaging
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CRM	Continual reassessment method
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic cell
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form

EDC	Electronic data capture
ECOG	Eastern Cooperative Oncology Group
EIH	Entry-into-human
EoT	End of treatment
ESCC	Esophageal squamous cell carcinoma
EU	European Union
EWOC	Escalation with overdose control
FAP	Fibroblast activation protein- α
FDA	Food and Drug Administration
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
HDL	High-density lipoproteins
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
HNSCC	Head and neck squamous cell carcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IMC	Internal Monitoring Committee
imAE	Immune-mediated adverse event
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRR	Infusion-related reactions
IRT	Interactive response system
IUD	Intrauterine device

IV	Intravenous
IxRS	Interactive (voice/web) response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LFT	Liver function tests
LH	Luteinizing hormone
mAb	Monoclonal antibody
MABEL	Minimal anticipated biological effect level
MAS	Macrophage activation syndrome
MD	Multiple doses
mCRM	Modified continual reassessment method
MHC I	Major histocompatibility complex I
mPAD	Minimal pharmacologically active dose
MoA	Mode of action
MRI	Magnetic resonance imaging
MSLN	Mesothelin
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next generation sequencing
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
pADA	Pre-existing anti-drug antibody
pANCA	Perinuclear anti-neutrophil cytoplasmic antibody
PD	Pharmacodynamic
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
popPK	Population pharmacokinetics

PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Every 3 weeks
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red blood cell
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RDE	Recommended dose for expansion
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SCLC	Small-cell lung cancer
SD	Stable disease
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
<i>SITC</i>	<i>Society for Immunotherapy of Cancer</i>
SoA	Schedule of assessment
SoC	Standard of care
$t_{1/2}$	Terminal half-life
T3	Triiodothyronine
T4	Thyroxine
TC	Ternary complex
t_{max}	Time of maximum concentration observed
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
TTE	Transthoracic echocardiogram
ULN	Upper limit of normal
US	United States
V	Volume
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, DOSE-ESCALATION AND EXPANSION, PHASE I STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, AND ANTI-TUMOR ACTIVITY OF RO7300490, A FIBROBLAST ACTIVATION PROTEIN- α (FAP) TARGETED CD40 AGONIST, AS SINGLE AGENT OR IN COMBINATION WITH ATEZOLIZUMAB IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS

SHORT TITLE A PHASE I STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, AND ANTI-TUMOR ACTIVITY OF RO7300490 AS SINGLE AGENT OR IN COMBINATION WITH ATEZOLIZUMAB IN ADVANCED AND/OR METASTATIC SOLID TUMORS

PROTOCOL NUMBER: WP42627

VERSION: 3

TEST PRODUCT: RO7300490, atezolizumab, tocilizumab

PHASE: I

RATIONALE

In the past two decades, cancer immunotherapy has paved the way to improved treatment modalities for several cancer indications. However, despite the progress made, more is needed, largely because of the complex interplay of multiple dysregulated immune processes within the tumor environment.

RO7300490 is a second generation, bi-specific fibroblast activation protein- α (FAP)-targeted CD40 agonist, humanized, immunoglobulin (Ig)G1-based monoclonal antibody (mAb), whose agonistic activity is strictly dependent on FAP cross-linking. RO7300490 is being developed to overcome the narrow therapeutic index of non-targeted agonistic CD40 mAbs and achieve stronger activation of antigen-presenting cells (APCs) within the tumor microenvironment of [REDACTED] solid tumors while reducing off-target peripheral effects. RO7300490 is expected to show a safe profile and contribute as a valuable combination partner for the treatment of patients with a wide range of [REDACTED] solid tumors.

This entry-into-human (EIH), Phase I study aims to establish the safety, tolerability, pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of RO7300490 (alone or in combination with atezolizumab) and to evaluate its anti-tumor activity in patients with advanced and/or metastatic solid tumors.

OBJECTIVES AND ENDPOINTS

• Objectives	• Endpoints
• Primary	
<ul style="list-style-type: none"> To evaluate the safety and tolerability profile of RO7300490 as a single agent (Part 1) or in combination with atezolizumab (Part 2) 	<ul style="list-style-type: none"> Incidence, nature, and severity of adverse events (AEs) graded according the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for cytokine release syndrome (CRS)
<ul style="list-style-type: none"> To determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of RO7300490 as a single agent (Part 1) or in combination with atezolizumab (Part 2) 	<ul style="list-style-type: none"> Nature and frequency of dose-limiting toxicities (DLTs)
<ul style="list-style-type: none"> To assess the anti-tumor activity of RO7300490 in combination with atezolizumab [REDACTED] (Part 3) 	<ul style="list-style-type: none"> Objective response rate (ORR) According to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
• Secondary	
<ul style="list-style-type: none"> To characterize the pharmacokinetics (PK) profile of RO7300490 as a single agent (Part 1) and in combination with atezolizumab (Parts 2 and 3) 	<ul style="list-style-type: none"> PK profiles and parameters of RO7300490 after intravenous (IV) administration (e.g. area under the curve [AUC], minimum concentration [C_{min}], maximum concentration [C_{max}], clearance [CL], volume of distribution at steady-state conditions [V_{ss}])
<ul style="list-style-type: none"> To evaluate the anti-RO7300490 immune response to RO7300490 treatment (Parts 1, 2, and 3) 	<ul style="list-style-type: none"> Incidence and titer of RO7300490 anti-drug antibodies (ADA) during the study relative to prevalence of pre-existing ADA (pADA) at baseline
<ul style="list-style-type: none"> To assess the anti-tumor activity of RO7300490 alone (Part 1) and in combination with atezolizumab (Part 2) 	<ul style="list-style-type: none"> ORR Disease control rate (DCR) Duration of response (DoR) Progression-free survival (PFS; on-treatment) <p>All according to RECIST v1.1 by Investigator's assessment</p>
<ul style="list-style-type: none"> To assess the anti-tumor activity of RO7300490 in combination with atezolizumab [REDACTED] (Part 3) 	<ul style="list-style-type: none"> DCR DoR PFS <p>All according to RECIST v1.1 by Investigator's assessment</p>

• Objectives	• Endpoints
<ul style="list-style-type: none"> To evaluate the safety and tolerability of RO7300490 in combination with atezolizumab [REDACTED] Part 3) 	<ul style="list-style-type: none"> Incidence, nature, and severity of AEs graded according to the NCI CTCAE v5.0 and according to ASTCT Consensus Grading for CRS
<ul style="list-style-type: none"> To evaluate the potential effects of RO7300490 ADA and pADA 	<ul style="list-style-type: none"> Analysis of relationship between ADA/pADA incidence and safety, PK, or pharmacodynamic (PD) endpoints

OVERALL DESIGN

Study Design

This is an ELH, open-label, multicenter, multiple-ascending dose-escalation and expansion, Phase I clinical study of RO7300490 as single agent or in combination with atezolizumab.

The study consists of three parts:

- Part 1: dose-escalation of RO7300490 as a single agent.
- Part 2: dose-escalation of RO7300490 in combination with atezolizumab.
- Part 3: dose-expansion of RO7300490 in combination with atezolizumab in selected cancer types. [REDACTED]

[REDACTED] and implemented with an amendment to the protocol.

Part 2 will start after RO7300490 has demonstrated acceptable safety and tolerability, and favorable PK/PD properties as single agent in Part 1, and once evidence of efficacy and/or mode of action (MoA) of RO7300490 has been established. In the event that this evidence is available before Part 1 is completed (RO7300490 maximum tolerated dose [MTD] or recommended dose for expansion [RDE] determined), Part 1 and Part 2 may run in parallel, if concurrent enrollment is supported by safety and PK/PD data.

Part 3 will be initiated after the MTD or RDE of RO7300490 in combination with atezolizumab (Part 2) is defined.

At least 3 evaluable participants will be enrolled in each cohort during the dose-escalation in Parts 1 and 2. If deemed necessary to further characterize the safety, PK, and/or PD profile of RO7300490, additional participants may be enrolled after agreement between Investigators and the Sponsor at the doses already tested or in additional cohorts at doses that have not been explored for the determination of the MTD.

It is planned to mandate tumor biopsies (at screening and on-treatment) and archival tumor sample collection (if available) for all participants in Part 1 and Part 2, in order to investigate RO7300490 MoA. [REDACTED]

[REDACTED] Tumor tissue is collected in order to characterize treatment-induced PD effects of RO7300490, alone or in combination, in the tumor microenvironment and to validate PK/PD model assumptions.

For participants enrolling in Part 3, [REDACTED]

The assignment of participants to a cohort will be randomized when several cohorts (e.g., dose-escalation cohorts [Parts 1 and 2]) enroll simultaneously.

Treatment Groups and Duration

Part 1: RO7300490 single agent dose-escalation

Participants will receive escalating doses of RO7300490 via intravenous (IV) infusion as a single agent. RO7300490 will be initially administered every 2 weeks (Q2W), for up to 24

months maximum or until progressive disease, unacceptable toxicities, death, or withdrawal of consent. For participants on this treatment schedule, the cycle length is 14 days. If justified by emerging safety, PK and PD, and efficacy data, the Sponsor (in agreement with Investigators) may modify the drug administration frequency to every 3 weeks (Q3W). For participants on this modified treatment schedule, the cycle length is 21 days.

Intra-participant dose-escalation

To minimize the exposure of participants to suboptimal doses of RO7300490, intra-participant dose-escalation may be permitted after the second on-treatment tumor assessment has been performed, as indicated in the schedule of assessments (SoAs). If there are no major safety concerns, a participant may receive a higher RO7300490 dose, up to a dose that has been considered safe within the participant's dosing schedule, and which is at least one dose level below the highest current evaluated dose in Part 1, or up to the MTD, if reached. Once the participant has received the higher dose without experiencing an AE that meets the definition of a dose-limiting toxicity (DLT) or that requires post-administration hospitalization, he/she may be eligible for further escalations, as higher cleared dose levels become available.

All intra-participant dose-escalation decisions will be made by the Sponsor in consultation with the Investigator.

[REDACTED]

Part 2: RO7300490 dose-escalation in combination with atezolizumab

Participants will receive escalating doses of RO7300490 in combination with a fixed dose of atezolizumab IV. The starting dose of RO7300490 will be determined based on the evaluation of the emerging data from Part 1 that is available at the time of starting Part 2. The starting dose in Part 2 will be initiated at least one dose level below the highest dose already cleared during the dose-escalation in Part 1.

[REDACTED]

For participants on this treatment schedule, the cycle length is 14 days. If justified by emerging safety, PK, PD and efficacy data, the Sponsor may modify the frequency of RO7300490 administration to Q3W. In that case, atezolizumab will be administered Q3W at a dose of 1200 mg. For participants on this modified treatment schedule, the cycle length is 21 days.

Part 3: RO7300490 in combination with atezolizumab [REDACTED] [REDACTED] and implemented with an amendment) — dose-expansion in tumor-specific cohorts

[REDACTED]

Imaging sub-study: In addition to the main study (Parts 1, 2, and 3), an immuno-positron emission tomography (PET) imaging sub-study is planned to assess the tumor accumulation and tissue bio-distribution of RO7300490 using [⁸⁹Zr]-labeled RO7300490 as a radiotracer. This imaging sub-study will be initiated soon after the main study WP42627 has started and will only be conducted in the European Union (EU).

Participants who have completed the imaging sub-study will be eligible to receive RO7300490 single agent in Part 1 of the WP42627 main study from Cycle 2 Day 1 (C2D1) onwards. A direct move from the imaging sub-study to Part 2 may also be considered, provided Part 2 is already enrolling and the RO7300490/atezolizumab combination dose under consideration has been

assessed as safe. Decision to transfer to the main study will be made by the Sponsor in consultation with the Investigator.

The IMPs are: RO7300490 (starting dose 16 mg, IV), atezolizumab (840 mg Q2W or 1200 mg Q3W, IV), and tocilizumab (8 mg/kg for participants with a weight ≥ 30 kg or 12 mg/kg for participants with a weight <30 kg; maximum dose 800 mg, IV).

Tocilizumab will be considered as rescue medications only, which may be used (if needed) after the administration of RO7300490 for the treatment of severe or life-threatening CRS.

Length of Study

The maximum duration in the study for each participant will be 27 months, divided as follows:

- Screening: Days -28 to -1.
- Treatment Period: Maximum duration of 24 months from C1D1 until the last dose of study treatment (may be modified by the Sponsor if supported by emerging data).
- Safety follow-up: 60 days (± 7 days) after the last dose of study treatment.
- Survival follow-up: 3-monthly (± 14 days) after the last dose of study treatment (period not considered for the calculation of the maximum study duration).

End of Study

The end of this study is defined as the date when the last participant, last visit occurs or the date at which the last data point required for statistical analysis or protocol-defined safety follow-up for the last participant is received, whichever is the latest date. A participant is considered to have completed the study if he/she has completed all phases of the study, including the scheduled safety follow-up visit after the last dose of study treatment, also in case of premature treatment discontinuation.

PARTICIPANT POPULATION

The participants in this study will be adult patients diagnosed with locally [REDACTED] solid tumors [REDACTED]

Key Inclusion Criteria (for details, see Section 5.1 of the protocol)

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

- Signed informed consent form.
- Age ≥ 18 years.
- Life expectancy of ≥ 12 weeks.
- Histologically confirmed diagnosis of locally advanced and/or metastatic solid tumors that are not amenable to standard therapy.
- **For Part 1 and Part 2:** diagnosis of locally advanced and/or metastatic solid tumor types including: non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), triple-negative breast cancer (TNBC), cutaneous melanoma, *urothelial cancer (including renal pelvis, ureters, urinary bladder and urethra)*, mesothelioma, hepatocellular carcinoma (HCC), head and neck squamous cell carcinoma (HNSCC), esophageal squamous cell carcinoma (ESCC), and cervical squamous cell carcinoma (SCC).
- Radiologically measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Eastern Cooperative Oncology Group Performance Status 0-1.

- **For participants enrolled in Part 1 and Part 2 (only in cohorts with mandatory biopsies):** willingness to provide mandatory fresh screening and on-treatment biopsies as well as archival tumor samples acquired within ≤ 12 months (when available) from a safely accessible site, per Investigator determination and patient consent, provided the patient has more than one measurable target lesion. The biopsied lesion must not be a target lesion.
- **For participants enrolled in Part 3:** [REDACTED]
- Adequate bone marrow and organ functions.
- Adequate contraception.

Key Exclusion Criteria (for details, see Section 5.2 of the protocol)

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

- Known central nervous system (CNS) primary tumors or metastases, including leptomeningeal metastases, unless they have been previously treated *and* are asymptomatic, *are stable (without evidence of progression by computed tomography (CT) or magnetic resonance imaging (MRI) for at least 28 days prior to the first dose of the study drug)* and have had no requirement for systemic steroids or enzyme-inducing anticonvulsants in the last 14 days prior to screening.
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 14 days before Cycle 1 Day 1 (C1D1).
- Active second *invasive* malignancy *within two years prior to screening* (see Section 5.2 for *exceptions*).
- All acute toxic effects of any prior radiotherapy, chemotherapy, targeted or checkpoint inhibitor therapy or surgical procedure must have resolved to Grade ≤ 1 or returned to baseline, except for alopecia (any grade), for Grade 2 clinically controlled sequelae of immune-related toxicities related to checkpoint-inhibitor therapy like adrenal insufficiency and hypopituitarism, and for Grade 2 peripheral neuropathy.
- Significant cardiovascular/cerebrovascular disease within 6 months prior to C1D1 of study drug administration (see Section 5.2 for details).
- Known hereditary or acquired coagulopathies (e.g., hemophilia, von Willebrand disease, clinically manifested cancer-associated diffuse intravascular coagulation).
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug-induced), interstitial lung disease, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active interstitial lung disease /pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Severe dyspnea at rest or requiring supplementary oxygen therapy.
- Known clinically significant liver disease including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease.
- Active or history of autoimmune disease including, but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (*see Section 5.2 for exceptions*).
- Known active or uncontrolled bacterial, viral, fungal, mycobacterial, parasitic, or other infection at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization within 28 days prior to the start of study drug administration.
- Known human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection at screening.
- History of severe allergic or anaphylactic reactions to mAb therapy (or recombinant antibody-related fusion proteins).

- Known hypersensitivity to any of the components of RO7300490 formulation or to components of atezolizumab formulation.
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation.
- Pregnancy, lactation, or breastfeeding.
- Dementia or altered mental status that would prohibit informed consent.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug.
- Major surgery or significant traumatic injury within 28 days prior to the first study drug administration (excluding biopsies) or anticipation of the need for major surgery during study treatment.
- Treatment with radiotherapy, chemotherapy, hormonal therapy, targeted therapy, immunotherapy or investigational drug (defined as a treatment for which there is currently no regulatory authority–approved indication) concurrent or within 28 days or 5 half-lives of the drug (whichever is shorter) before the first study drug administration (C1D1).
- Previous treatment with any other compound that targets CD40 (e.g. selicrelumab [RO7009789], Chi Lob 7/4, mitazalimab [ADC-1013]).
- Regular immunosuppressive therapy or treatment with systemic immunosuppressive medications (including, but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 14 days prior to first study drug administration (*see Section 5.2 for exceptions*).
- Treatment with systemic immune-modulating agents, including but not limited to etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, or efalizumab) within 28 days or 5 half-lives of the drug (whichever is shorter) before the first study drug administration (C1D1).
- Radiotherapy within the last 28 days before the first study drug administration, with the exception of limited field palliative radiotherapy.
- Administration of a live, attenuated vaccine within 28 days prior to the first study drug administration.

NUMBER OF PARTICIPANTS

It is anticipated that at most 280 evaluable participants will be enrolled in Parts 1, 2, and 3 of this study:

The exact sample size in Part 1 (dose-escalation of RO7300490 as a single agent) and Part 2 (dose-escalation of RO7300490 in combination with atezolizumab) of the study will depend on the number of cohorts needed to reach the MTD and/or RDE. According to the modified continual reassessment method with escalation with overdose control (mCRM-EWOC) design, each part may require at most 60 participants for the dose-escalation.

The design for the Part 1 extension cohorts [REDACTED] approximately 40 participants may be enrolled in the Part 1 extension cohorts.

Part 3 (dose-expansion of RO7300490 in combination with atezolizumab [REDACTED])

CONCOMITANT MEDICATIONS

In general, no concomitant medication will be permitted, with the exception of medications to treat AEs and therapy for pre-existing conditions, unless the rationale for exception is discussed and clearly documented between Investigator and the Sponsor.

For a list of prohibited therapies within 28 days prior to RO7300490 and/or atezolizumab administration, refer to the exclusion criteria.

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, targeted therapy, hormonal therapy, immunotherapy, radiotherapy, radio-immunotherapy.
- Radiotherapy may be considered for pain palliation.

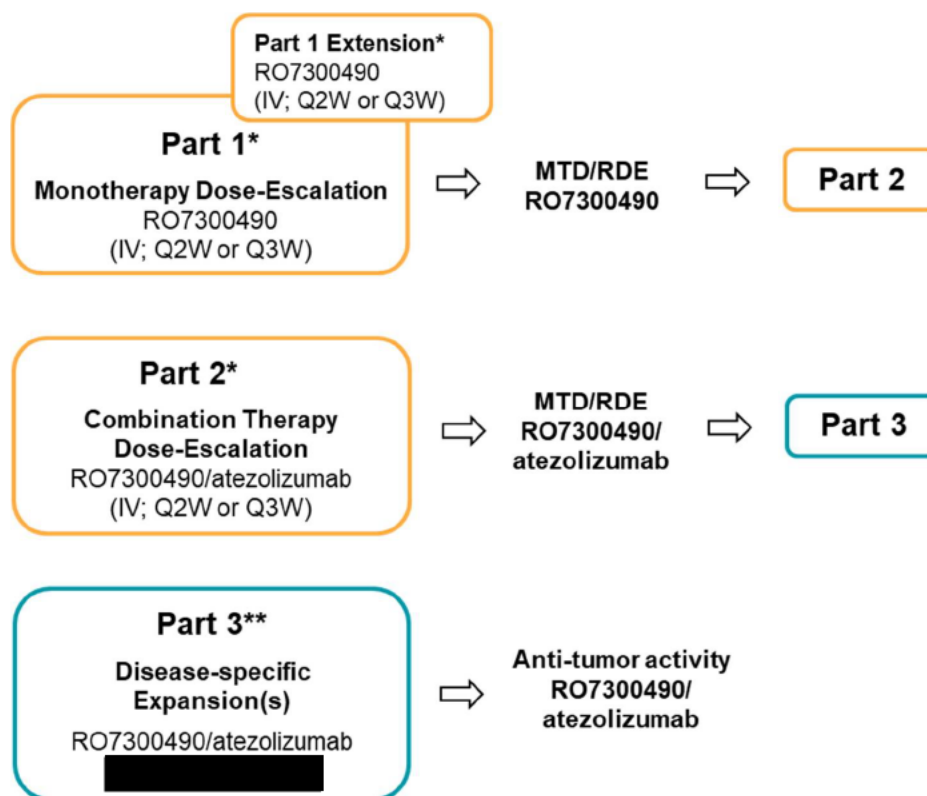
The following therapies are prohibited while participants are receiving RO7300490 and/or atezolizumab:

- Immunostimulatory agents (including, but not limited to, interferons or IL-2).
- Immunosuppressive medications including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide.
- 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 (as per institutional guidelines). Acute and/or low-dose systemic immunosuppressive medications (e.g. a one-time dose of dexamethasone for nausea *or 48 hours maximum of corticosteroids as premedication for a contrast allergy* or chronic use of ≤ 10 mg/day of prednisone or another dose-equivalent corticosteroid) *are* allowed.
- Administration of a live, attenuated vaccine.
- Metamizole (dipyrone) is prohibited to treat atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in [Figure 1](#).

Figure 1 Overview of Study Design



Abbreviations: ██████████ IV = Intravenously; MTD = Maximum tolerated dose; Q2W = Every 2 weeks; Q3W = Every 3 weeks; RDE = Recommended dose for expansion; ██████████

* For all participants in Part 1 and Part 2, ██████████ collection of fresh tumor biopsies (at screening and on-treatment) and archival tumor sample (when available) is mandatory. One or more cohorts enrolling at this and potentially further RO7300490 doses (lower and/or higher), may be extended with additional participants (Part 1 extension cohorts)

**For Part 3, ██████████
Part 2 will start after RO7300490 has demonstrated acceptable safety and tolerability, and favorable PK/PD properties as single agent in Part 1, and once evidence of efficacy and/or mode of action (MoA) of RO7300490 has been established. In the event that this evidence is available before Part 1 is completed (RO7300490 maximum tolerated dose [MTD] or recommended dose for expansion [RDE] determined), Part 1 and Part 2 may run in parallel, if concurrent enrollment is supported by safety and PK/PD data. Part 3 will be initiated after the MTD or RDE of RO7300490 in combination with atezolizumab is defined in Part 2.

1.3 SCHEDULE OF ASSESSMENTS

The schedule of the assessments (SoAs) are provided in [Table 1](#), [Table 2](#), [Table 3](#), and [Table 4](#).

Table 1 Schedule of Assessments for Part 1 and Part 2: Main Table for Q2W Dosing

Protocol Section	Cycle (14 days)	Screening	Cycle 1					Cycle 2				Cycle 3				Cycle 4				Cycle 5		Subsequent Cycles	End of Treatment Visit ^a	Safety Follow-Up Visit	Survival Follow-Up by Phone	Unscheduled Visit ^b	
7.1.1	Study Visit Window	D-28 to D-1	±1 day ±1 day +1 day ±1 day +1 day					±1 day +1 day				±1 day +1 day				+3 days ±1 day		+3 days	within 30 days after last study treatment dose	±7 days	±14 days						
	Day (D; relative to study drug administration)		D 1	D 2	D 3	D 5	D 8	D 1	D 2	D 8	D 1	D 2	D 3	D 8	D 1	D 2	D 3	D 8					D 1	D 8	D1		
Clinical Assessments																											
Appendix 1	Written informed consent	x																									
5.1.5.2	Eligibility	x																									
Appendix 1	Written consent for RBR (optional)	x																									
8.2.6	Demography	x																									
8.2.6	Medical and cancer history	x																									
8.2.1	Physical examination	x	x					x			x				x				x		x		x			x	
8.2.1	Height	x																									
8.2.1	Weight	x (D-14 to D-1)	x								x				x				x		x		x				
8.2.3	ECOG performance status	x	x					x			x				x				x		x		x			x	
8.2.2	Vital signs ^c (incl. pre-/post-infusion; during infusion)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	
8.2.4	Triplicate 12-lead ECG (incl. pre-/post-infusion)	x (D-14 to D-1)	x								x				x				x		x		x				
5.1	Echocardiography (MUGA/TTE/cMRI), if applicable	x																									
8.1.1	CT or MRI of the head	x																									
8.2.6	Previous and concomitant treatments	x													x								x			x	
8.3	Adverse events (AEs)														x								x			x	
8.1.1, 8.1.2	Tumor assessment (CT/MRI with contrast of chest, abdomen, and pelvis; digital photography if applicable)	x	At week 6 (+7d), week 12 (+7d), week 18 (+7d) and then every 12 weeks (i.e. week 30, week 42, etc.; [±7 days]) until disease progression, initiation of a post-study anti-cancer therapy, withdrawal or death. At the Investigator's discretion, tumor assessment may be repeated at any time if progressive disease is suspected.																								
8.1.1	Pre-study CT/MRI scan (optional)	W-12 to D-29																									
8.2.6	Post-study anti-cancer therapies																							x		x	
Local Laboratory Assessments																											
8.2.5, Appendix 4	Hematology	x (D-14 to D-1)	x ^d	x				x	x ^d	x	x	x	x ^d	x	x	x	x ^d	x	x	x ^d	x	x	x ^d	x			x
8.2.5, Appendix 4	Clinical chemistry	x (D-14 to D-1)	x ^d	x				x	x ^d	x	x	x	x ^d	x	x	x	x ^d	x	x	x ^d	x	x	x ^d	x			x
8.2.5, Appendix 4	Coagulation	x (D-14 to D-1)	x ^d	x				x	x ^d	x	x	x	x ^d	x	x	x	x ^d	x	x	x ^d	x	x	x ^d	x			x
8.2.5, Appendix 4	Urinalysis	x (D-14 to D-1)	x ^d						x ^d				x ^d			x ^d				x ^d		x ^d		x			x
8.2.5, Appendix 4	Viral serology	x																									
8.2.5, Appendix 4	Lipids	x	Every 8 weeks (±7 days) after C1D1																								
8.2.5, Appendix 4	Thyroid function	x	Every 8 weeks (±7 days) after C1D1																								
8.2.5, Appendix 4	Auto-antibody panel	x	As clinically indicated																								
8.2.5, Appendix 4	IgE and tryptase		In the event of Grade ≥ 3 RR/CRS, or Grade ≥ 2 hypersensitivity reaction																								
Appendix 5 (point 3)	Pregnancy test	serum (D-14 to D-1)	urine ^e (serum if positive)																urine ^{d,e} (serum if positive)					C7D1 then D1 of every 2 cycles ^{d,e} urine (serum if positive)	serum	serum	
Study Treatment Administration																											
6.1.1	RO7300490		x						x					x					x				x				
6.1.2	Atezolizumab (only in Part 2)		x						x					x					x				x				
6.1.3	Tocilizumab (TCZ)																										
If needed for the treatment of CRS, refer to TCZ SoA in Appendix 11 for detailed assessments																											
Central Laboratory Assessments																											
8.8.1.2	Archival tumor sample (if available)	x ^f																									
8.8.1.2	Fresh tumor biopsy	x ^f																									
8.5	Serum PK RO7300490																							x		x	
8.6	Serum ADA RO7300490																							x		x	
8.5	Serum PK atezolizumab																									x (only in Part 2)	
8.6	Serum ADA atezolizumab																									x (only in Part 2)	
8.8.1.1	Blood receptor occupancy (flow cytometry)		Refer to the hourly schedule of assessments for sampling details																								
8.8.1.1	Whole blood TBNK (flow cytometry)																										
8.8.1.1	Plasma PD (cytokines)																										
8.9.1	Blood RBR (DNA and RNA) - optional	x ^g																								x	

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Table 1 Schedule of Assessments for Part 1 and Part 2: Main Table for Q2W Dosing (cont.)

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; C = Cycle; cMRI = Cardiac magnetic resonance imaging; CT = Computed tomography; CRS = Cytokine release syndrome; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = End of infusion; IgE = Immunoglobulin E; IRR = Infusion-related reaction; MRI = Magnetic resonance imaging; MTD = maximum tolerated dose; MUGA = Multigated acquisition scan; PD = Pharmacodynamics; PK = Pharmacokinetic; RBR = Research Biosample Repository; RDE = Recommended dose for expansion; Q2W = Every two weeks; SoA = Schedule of assessments; TCZ = Tocilizumab; TNBK = T cell, B cell, NK cell; TTE = Transthoracic echocardiogram; W = Week.

- a) The visit at which response assessment shows progressive disease, or at which the participant is discontinued, or withdraws from the study may be used as EoT visit.
- b) If clinically indicated, any assessment or sample specified in the SoA can be performed any time as unscheduled assessment or sample at the discretion of the Investigator. If the unscheduled visit is conducted for the following safety reasons (participant experiences a suspected Grade ≥ 3 IRR/CRS, or Grade ≥ 3 hypersensitivity reaction, or RO7300490-related Grade ≥ 2 AE leading to treatment interruption/discontinuation or delay), assessments marked in the table must be performed and PK, ADA, and PD samples for cytokines and receptor occupancy will be taken. Of note, for participants who transferred from the imaging sub-study, only PK/ADA samples and plasma sample for cytokines (safety) will be collected in such instance. The PK/ADA/PD samples should be taken as soon as possible (i.e., ideally at the time of the development of such an event or, if not feasible, at the earliest possible convenience). If unscheduled PK/ADA/PD sampling time points fall during overnight hours and staff is not available for collecting/processing samples, collection can be delayed until the following morning. Every attempt should be made to collect the samples at the earliest possible convenience. If PK/ADA/PD sample collection is delayed until the following morning, it is critical that the actual PK/ADA/PD sampling collection time and date be documented in the eCRF.
- c) Vital signs include temperature, heart rate, respiratory rate, and blood pressure. Vital signs should be taken after ECG when scheduled at the same time point, when possible. For schedule of measurements on dosing days, refer to protocol Section 8.2.2.
- d) Can be performed within 24 hours (up to 72 hours if during weekend or bank holiday) prior to scheduled dosing.
- e) If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (which may be performed with leftover from clinical chemistry sample).
- f) For all participants in Part 1 and Part 2 [REDACTED] which demonstrates favorable safety and preliminary anti-tumor activity or favorable PK/PD properties of RO7300490, collection of fresh tumor biopsies (at screening and on-treatment) and archival tumor sample (when available) is mandatory. On-treatment biopsy has to be collected on C3D3 (48 hours post-EOI \pm 6 hours). If the participant discontinues treatment before the scheduled on-treatment biopsy time point, a biopsy should be collected at the time of treatment discontinuation. Additional biopsy at time of partial response (PR), stable disease (SD), progressive disease or any other time point of interest based on the participant's course of disease may be taken after discussion between the Investigator and the Sponsor, and upon participant consent.
- g) Blood for RBR may also be collected on the first dosing day (C1D1) prior to dosing.

Table 2 Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Part 1 and Part 2: Hourly Table for Q2W Dosing

Cycle (14 days)	Day (D; relative to study drug administration)	Scheduled Time	Time Window	Serum sample for RO7300490 PK ^a	Serum sample for RO7300490 ADA ^a	Serum sample for atezolizumab PK ^a (only in Part 2)	Serum sample for atezolizumab ADA ^a (only in Part 2)	Blood receptor occupancy (flow cytometry)	Whole blood TBNK (flow cytometry)	Plasma PD (cytokines)	Fresh tumor biopsy ^f	Archival tumor sample ^g (if available)	Blood RBR (DNA and RNA) ^h (optional)
Protocol Section				8.5	8.6	8.5	8.6	8.8.1.1	8.8.1.1	8.8.1.1	8.8.1.2	8.8.1.2	8.9.1
Screening	D- 28 to D- 1										x	x	x
Cycle 1	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x	x	x	x			
		EOI (atezolizumab; Part 2 only)	+15 min			x							
		EOI (RO7300490)	+15 min	x									
		02h post EOI	±30 min	x				x					
		06h post EOI	± 2h	x									
	D2	24h post EOI	± 2h	x				x	x	x			
	D3	48h post EOI	± 6h	x				x	x	x			
	D5	96h post EOI	± 24h	x					x				
Cycle 2	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x	x	x	x			
		EOI (atezolizumab; Part 2 only)	+15 min			x							
		EOI (RO7300490)	+15 min	x									
		02h post EOI	±30 min	x				x					
		06h post EOI	± 2h	x									
	D2	24h post EOI	± 2h	x				x	x				
	D8	168h post EOI	± 24h	x		x		x	x	x			
Cycle 3	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x	x	x				
		EOI (atezolizumab; Part 2 only)	+15 min			x							
		EOI (RO7300490)	+15 min	x									
		06h post EOI	± 2h	x									
	D3	48h post EOI	± 6h								x		
Cycle 4	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x	x	x				
		EOI (atezolizumab; Part 2 only)	+15 min			x							
		EOI (RO7300490)	+15 min	x									
		02h post EOI	±30 min	x									
		06h post EOI	± 2h	x									
	D2	24h post EOI	± 2h	x									
	D3	48h post EOI	± 6h	x									
	D8	168h post EOI	± 24h	x									
Cycle 5 - Cycle 8	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x		x				
		EOI (RO7300490)	+15 min	x									
Cycle 9 onwards ^c	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x		x				
		EOI (RO7300490)	+15 min	x									
End of Treatment Visit ^d	within 30 days after last study treatment dose			x	x		x						
Safety Follow up Visit	60 days post last study treatment dose (±7 days)				x		x						
Unscheduled Visit ^e				x	x	x	x	x		x			

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Table 2 Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Part 1 and Part 2: Hourly Table for Q2W Dosing (cont.)

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; C = Cycle; CRS = Cytokine release syndrome; D = Day; eCRF = Electronic case report form; EOI = End of infusion; IRR = Infusion-related reaction; IV = Intravenous; MTD = maximum tolerated dose; PD = Pharmacodynamics; PK = Pharmacokinetic; Q2W = Every two weeks; RBR = Research Biosample Repository; TBNK = T cell, B cell, NK cell.

- a) All blood samples for PK/ADA assessments will be collected from an IV line sited in a different location to that used for drug infusion (e.g. opposite arm). If feasible, the line will remain in place until the 24-hour sample is taken. If due to late drug administration times, PK sampling time points fall during overnight hours and staff is not available for collecting/processing samples, collection can be delayed until the following morning. Every attempt should be made to timely collect pre-infusion and EOI samples as these are very important for characterizing the minimal and maximal drug concentration in serum, respectively. If a PK samples is delayed to the following morning, it is critical that the actual PK sampling collection time and date is documented in the eCRF.
- b) The pre-infusion PK, PD and ADA samples can be obtained up to 24 hours (exceptionally up to 72 hours in case of bank holiday) prior to treatment administration on C1D1 and all subsequent cycles.
- c) Starting C9, every second cycle (C9, C11, C13, etc.).
- d) The visit at which response assessment shows progressive disease, or at which the participant is discontinued, or withdraws from the study may be used as EoT visit.
- e) If the unscheduled visit is conducted for safety reasons (participant experiences a suspected Grade ≥ 3 IRR/CRS, or Grade ≥ 3 hypersensitivity reaction, or RO7300490-related Grade ≥ 2 AE leading to treatment interruption/discontinuation or delay), PK, ADA, and PD samples for cytokines and receptor occupancy will be collected. Of note, for participants who transferred from the imaging sub-study, only PK/ADA samples and plasma sample for cytokines (safety) will be collected in such instance. The PK/ADA/PD samples should be taken as soon as possible (i.e., ideally at the time of the development of such an event or, if not feasible, at the earliest possible convenience). If unscheduled PK/ADA/PD sampling time points fall during overnight hours and staff is not available for collecting/processing samples, collection can be delayed until the following morning. Every attempt should be made to collect the samples at the earliest possible convenience. If PK/ADA/PD sample collection is delayed until the following morning, it is critical that the actual PK/ADA/PD sampling collection time and date be documented in the eCRF.
- f) For all participants in Part 1 and Part 2, [REDACTED] which demonstrates favorable safety and preliminary anti-tumor activity or favorable PK/PD properties of RO7300490, collection of fresh tumor biopsies (at screening and on-treatment) and archival tumor sample (when available) is mandatory. On-treatment biopsy has to be collected on C3D3 (48 hours post-EOI \pm 6 hours). If the participant discontinues treatment before the scheduled on-treatment biopsy time point, a biopsy should be collected at the time of treatment discontinuation. Additional biopsy at time of partial response (PR), stable disease (SD), progressive disease, or any other time point of interest based on the participant's course of disease may be taken after discussion between the Investigator and the Sponsor, and upon participant consent.
- g) Blood for RBR may also be collected on the first dosing day (C1D1) prior to dosing.

Table 3 Schedule of Assessments for Part 1 and Part 2: Main Table for Q3W Dosing

Protocol Section	Cycle (21 days)	Screening	Cycle 1						Cycle 2				Cycle 3					Cycle 4					
7.1.1	Study Visit Window	D-28 to D-1				±1 day	±1 day	±1 day	+1 day	±1 day		±1 day	+1 day			±1 day	±1 day	+1 day			±1 day	±1 day	
	Day (D; relative to study drug administration)		D 1	D 2	D 3	D 5	D 8	D 15	D 1	D 2	D 8	D 15	D 1	D 2	D 3	D 8	D 15	D 1	D 2	D 3	D 8	D 15	
Clinical Assessments																							
Appendix 1	Written informed consent	x																					
5.1, 5.2	Eligibility	x																					
Appendix 1	Written consent for RBR (optional)	x																					
8.2.6	Demography	x																					
8.2.6	Medical and cancer history	x																					
8.2.1	Physical examination	x	x						x				x					x					
8.2.1	Height	x																					
8.2.1	Weight	x (D-14 to D-1)	x						x				x					x					
8.2.3	ECOG performance status	x	x						x				x					x					
8.2.2	Vital signs ^c (incl. pre-/post-infusion; during infusion)	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x		
8.2.4	Triplicate 12-lead ECG (incl. pre-/post-infusion)	x (D-14 to D-1)	x						x				x					x					
5.1	Echocardiography (MUGA/TTE/cMRI), if applicable	x																					
8.1.1	CT or MRI of the head	x																					
8.2.6	Previous and concomitant treatments	x																					
8.3	Adverse events (AEs)		x																				
8.1.1, 8.1.2	Tumor assessment (CT/MRI with contrast of chest, abdomen, and pelvis; digital photography if applicable)	x	On week 6 (+7d), week 12 (+7d), week 18 (+7d) and then every 12 weeks (i.e. week 30, week 42, etc.; [±7 days]) until disease progression, initiation of a post-study anti-cancer therapy, withdrawal or death. At the Investigator's discretion, tumor assessment may be repeated at any time if progressive disease is suspected.																				
8.1.1	Pre-study CT/MRI scan (optional)	W-12 to D-29																					
8.2.6	Post-study anti-cancer therapies																						
Local Laboratory Assessments																							
8.2.5, Appendix 4	Hematology	x (D-14 to D-1)	x ^d	x			x	x	x ^d	x	x	x	x ^d	x		x	x	x ^d	x		x	x	
8.2.5, Appendix 4	Clinical chemistry	x (D-14 to D-1)	x ^d	x			x	x	x ^d	x	x	x	x ^d	x		x	x	x ^d	x		x	x	
8.2.5, Appendix 4	Coagulation	x (D-14 to D-1)	x ^d	x			x	x	x ^d	x	x	x	x ^d	x		x	x	x ^d	x		x	x	
8.2.5, Appendix 4	Urinalysis	x (D-14 to D-1)	x ^d						x ^d				x ^d					x ^d					
8.2.5, Appendix 4	Viral serology	x																					
8.2.5, Appendix 4	Lipids	x	every 8 weeks (±7 days) after C1D1																				
8.2.5, Appendix 4	Thyroid function	x	every 8 weeks (±7 days) after C1D1																				
8.2.5, Appendix 4	Auto-antibody panel	x	as clinically indicated																				
8.2.5, Appendix 4	IgE and tryptase		In the event of Grade ≥ 3 IR/CRS, or Grade ≥ 2 hypersensitivity reaction																				
Appendix 5 (Section 3)	Pregnancy test	serum (D-14 to D-1)	urine ^e (serum if positive)						urine ^{d,e} (serum if positive)				urine ^{d,e} (serum if positive)					urine ^{d,e} (serum if positive)					
Study Treatment Administration																							
6.1.1	RO7300490		x						x				x					x					
6.1.2	Atezolizumab (only in Part 2)		x						x				x					x					
6.1.3	Tocilizumab (TCZ)		If needed for the treatment of CRS; refer to TCZ SoA in Appendix 11 for detailed assessments																				
Central Laboratory Assessments																							
8.8.1.2	Archival tumor sample (if available)	x ^f																					
8.8.1.2	Fresh tumor biopsy	x ^f																x ^f					
8.5	Serum PK RO7300490		Refer to the hourly schedule of assessments for sampling details																				
8.6	Serum ADA RO730049																						
8.5	Serum PK atezolizumab																						
8.6	Serum ADA atezolizumab																						
8.8.1.1	Blood receptor occupancy (flow cytometry)																						
8.8.1.1	Whole blood TBNK (flow cytometry)																						
8.8.1.1	Plasma PD (cytokines)																						
8.9.1	Blood RBR (DNA and RNA) - optional	y ^g																					

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Table 3 Schedule of Assessments for Part 1 and Part 2: Main Table for Q3W Dosing (cont.)

Protocol Section	Cycle (21 days)	Cycle 5			Subsequent Cycles		End of Treatment visit ^a	Safety Follow- Up Visit	Survival Follow-Up by Phone	Unscheduled Visit ^b
7.1.1	Study Visit Window	+3 days	±1 day	±1 day	+3 days	±1 day		±7 days	±14 days	
	Day (D; relative to study drug administration)	D 1	D 8	D 15	D1	D 15	within 30 days after last study treatment dose	60 days post last study treatment dose	90 days post last dose, then every 3 months (±14 days)	
Clinical Assessments										
Appendix 1	Written informed consent									
5.1, 5.2	Eligibility									
Appendix 1	Written consent for RBR (optional)									
8.2.6	Demography									
8.2.6	Medical and cancer history									
8.2.1	Physical examination	x			x		x	x		x
8.2.1	Height									
8.2.1	Weight	x			x		x	x		
8.2.3	ECOG performance status	x			x		x	x		x
8.2.2	Vital signs ^c (incl. pre-/post-infusion; during infusion)	x	x	x	x	x	x	x		x
8.2.4	Triplicate 12-lead ECG (incl. pre-/post-infusion)	x			x		x	x		
5.1	Echocardiography (MUGA/TTE/cMRI), if applicable									
8.1.1	CT or MRI of the head									
8.2.6	Previous and concomitant treatments				x			x		x
8.3	Adverse events (AEs)				x			x		x
8.1.1, 8.1.2	Tumor assessment (CT/MRI with contrast of chest, abdomen, and pelvis; digital photography if applicable)	On week 6 (+7d), week 12 (+7d), week 18 (+7d) and then every 12 weeks (i.e. week 30, week 42, etc.; [±7 days]) until disease progression, initiation of a post-study anti-cancer therapy, withdrawal or death. At the Investigator's discretion, tumor assessment may be repeated at any time if progressive disease is suspected.								
8.1.1	Pre-study CT/MRI scan (optional)									
8.2.6	Post-study anti-cancer therapies							x	x	
Local Laboratory Assessments										
8.2.5, Appendix 4	Hematology	x ^d	x	x	x ^d	x	x	x		x
8.2.5, Appendix 4	Clinical chemistry	x ^d	x	x	x ^d	x	x	x		x
8.2.5, Appendix 4	Coagulation	x ^d	x	x	x ^d	x	x	x		x
8.2.5, Appendix 4	Urinalysis	x ^d			x ^d		x	x		x
8.2.5, Appendix 4	Viral serology									
8.2.5, Appendix 4	Lipids	every 8 weeks (±7 days) after C1D1					x	x		
8.2.5, Appendix 4	Thyroid function	every 8 weeks (±7 days) after C1D1					x	x		
8.2.5, Appendix 4	Auto-antibody panel	as clinically indicated								
8.2.5, Appendix 4	IgE and tryptase	In the event of Grade ≥ 3 IRR/CRS, or Grade ≥ 2 hypersensitivity reaction								
Appendix 5 (Section 3)	Pregnancy test	urine ^{d,e} (serum if positive)			D1 of every cycle ^{d,e} ; urine (serum if positive)		serum	serum		
Study Treatment Administration										
6.1.1	RO7300490	x			x					
6.1.2	Atezolizumab (only in Part 2)	x			x					
6.1.3	Tocilizumab (TCZ)	If needed for the treatment of CRS; refer to TCZ SoA in Appendix 11 for detailed assessments								
Central Laboratory Assessments										
8.8.1.2	Archival tumor sample (if available)									
8.8.1.2	Fresh tumor biopsy									
8.5	Serum PK RO7300490	Refer to the hourly schedule of assessments for sampling details					x			x
8.6	Serum ADA RO730049						x	x		x
8.5	Serum PK atezolizumab									x (only in Part 2)
8.6	Serum ADA atezolizumab						x (only in Part 2)	x (only in Part 2)		x (only in Part 2)
8.8.1.1	Blood receptor occupancy (flow cytometry)									x
8.8.1.1	Whole blood TBNK (flow cytometry)									
8.8.1.1	Plasma PD (cytokines)									
8.9.1	Blood RBR (DNA and RNA) - optional									

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Table 3 Schedule of Assessments for Part 1 and Part 2: Main Table for Q3W Dosing (cont.)

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; C = Cycle; cMRI = Cardiac magnetic resonance imaging; CT = Computed tomography; CRS = Cytokine release syndrome; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IgE = Immunoglobulin E; IRR = Infusion-related reaction; MRI = Magnetic resonance imaging; MTD = maximum tolerated dose; MUGA = Multigated acquisition scan; PD = Pharmacodynamics; PK = Pharmacokinetic; RBR = Research Biosample Repository; RDE = Recommended dose for expansion; Q3W = Every three weeks; SoA = Schedule of assessments; TCZ = Tocilizumab; TNBK = T cell, B cell, NK cell; TTE W = Week.

- a) The visit at which response assessment shows progressive disease, or at which the participant is discontinued, or withdraws from the study may be used as EoT visit.
- b) If clinically indicated, any assessment or sample specified in the SoA can be performed any time as unscheduled assessment or sample at the discretion of the Investigator. If the unscheduled visit is conducted for the following safety reasons (participant experiences a suspected Grade ≥ 3 IRR/CRS, or Grade ≥ 3 hypersensitivity reaction, or RO7300490-related Grade ≥ 2 AE leading to treatment interruption/discontinuation or delay), assessments marked in the table must be performed and PK, ADA, and PD samples for cytokines and receptor occupancy will be taken. Of note, for participants who transferred from the imaging sub-study, only PK/ADA samples and plasma sample for cytokines (safety) will be collected in such instance. The PK/ADA/PD samples should be taken as soon as possible (i.e., ideally at the time of the development of such an event or, if not feasible, at the earliest possible convenience). If unscheduled PK/ADA/PD sampling time points fall during overnight hours and staff is not available for collecting/processing samples, collection can be delayed until the following morning. Every attempt should be made to collect the samples at the earliest possible convenience. If PK/ADA/PD sample collection is delayed to the following morning, it is critical that the actual PK/ADA/PD sampling collection time and date be documented in the eCRF.
- c) Vital signs include temperature, heart rate, respiratory rate, and blood pressure. Vital signs should be taken after ECG when scheduled at the same time point, when possible. For schedule of measurements on dosing days, refer to protocol Section 8.2.2.
- d) Can be performed within 24 hours (up to 72 hours if during weekend or bank holiday) prior to scheduled dosing.
- e) If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (which may be performed with leftover from clinical chemistry sample).
- f) For all participants in Part 1 and Part 2, [REDACTED] which demonstrates favorable safety and preliminary anti-tumor activity or favorable PK/PD properties of RO7300490, collection of fresh tumor biopsies (at screening and on-treatment) and archival tumor sample (when available) is mandatory. On-treatment biopsy has to be collected on C3D3 (48 hours post-EOI \pm 6 hours). If the participant discontinues treatment before the scheduled on-treatment biopsy time point, a biopsy should be collected at the time of treatment discontinuation. Additional biopsy at time of partial response (PR), stable disease (SD), progressive disease or any other time point of interest based on the participant's course of disease may be taken after discussion between the Investigator and the Sponsor, and upon participant consent.
- g) Blood for RBR may also be collected on the first dosing day (C1D1) prior to dosing.

Table 4 Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Part 1 and Part 2: Hourly Table for Q3W Dosing

Cycle (21 days)	Day (D; relative to study drug administration)	Scheduled Time	Time Window	Serum sample for RO7300490 PK ^a	Serum sample for RO7300490 ADA ^a	Serum sample for atezolizumab PK ^a (only in Part 2)	Serum sample for atezolizumab ADA ^a (only in Part 2)	Blood receptor occupancy (flow cytometry)	Whole blood TBNK (flow cytometry)	Plasma PD (cytokines)	Fresh tumor biopsy ^f	Archival tumor sample ^f (if available)	Blood RBR (DNA and RNA) ^g (optional)
Protocol Section				8.5	8.6	8.5	8.6	8.8.1.1	8.8.1.1	8.8.1.1	8.8.1.2	8.8.1.2	8.9.1
Screening	D- 28 to D- 1										x	x	x
Cycle 1	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x	x	x	x			
		EOI (atezolizumab; Part 2 only)	+15 min			x							
		EOI (RO7300490)	+15 min	x									
		02h post EOI	±30 min	x				x					
		06h post EOI	± 2h	x									
	D2	24h post EOI	± 2h	x				x	x	x			
	D3	48h post EOI	± 6h	x				x	x	x			
	D5	96h post EOI	± 24h	x					x				
	D8	168h post EOI	± 24h	x		x		x	x	x			
	D15	336h post EOI	± 24h	x		x		x	x	x			
Cycle 2	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x	x	x	x			
		EOI (atezolizumab; Part 2 only)	+15 min			x							
		EOI (RO7300490)	+15 min	x									
		02h post EOI	±30 min	x				x					
		06h post EOI	± 2h	x									
	D2	24h post EOI	± 2h	x				x	x				
	D8	168h post EOI	± 24h	x				x	x				
Cycle 3	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x	x	x				
		EOI (atezolizumab; Part 2 only)	+15 min			x							
		EOI (RO7300490)	+15 min	x									
		06h post EOI	± 2h	x									
Cycle 4	D1	06h post EOI	± 2h	x									
		48h post EOI	± 6h								x		
		Pre-first infusion	up to 24h before ^b	x	x	x	x	x	x				
		EOI (atezolizumab; Part 2 only)				x							
		EOI (RO7300490)	+15 min	x									
	D2	02h post EOI	±30 min	x									
		06h post EOI	± 2h	x									
		24h post EOI	± 2h	x									
		48h post EOI	± 6h	x									
		168h post EOI	± 24h	x									
Cycle 5 - Cycle 8	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x		x				
		EOI (RO7300490)	+15 min	x									
Cycle 9 onward ^c	D1	Pre-first infusion	up to 24h before ^b	x	x	x	x		x				
		EOI (RO7300490)	+15 min	x									
End of Treatment Visit ^d	within 30 days after last study treatment dose			x	x		x						
Safety Follow-Up Visit	60 days post last study treatment dose (±7 days)				x		x						
Unscheduled Visit ^e				x	x	x	x	x		x			

Table 4 Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Part 1 and Part 2: Hourly Table for Q3W Dosing (cont.)

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; C = Cycle; CRS = Cytokine release syndrome; D = Day; eCRF = Electronic case report form; EOI = End of infusion; IRR = Infusion-related reaction; IV = Intravenous; MTD = maximum tolerated dose; PD = Pharmacodynamics; PK = Pharmacokinetic; Q3W = Every three weeks; RBR = Research Biosample Repository; TBNK = T cell, B cell, NK cell.

- a) All blood samples for PK/ADA assessments will be collected from an IV line sited in a different location to that used for drug infusion (e.g., opposite arm). If feasible, the line will remain in place until the 24-hour sample is taken. If due to late drug administration times, PK sampling time points fall during overnight hours and staff is not available for collecting/processing samples, collection can be delayed until the following morning. Every attempt should be made to timely collect pre-infusion and EOI samples as these are very important for characterizing the minimal and maximal drug concentration in serum, respectively. If a PK samples is delayed to the following morning, it is critical that the actual PK sampling collection time and date is documented in the eCRF.
- b) The pre-infusion PK, PD and ADA samples can be obtained up to 24 hours (exceptionally up to 72 hours in case of bank holiday) prior to treatment administration on C1D1 and all subsequent cycles.
- c) Starting C9, every second cycle (C9, C11, C13, etc.).
- d) The visit at which response assessment shows progressive disease, or at which the participant is discontinued, or withdraws from the study may be used as EoT visit.
- e) If the unscheduled visit is conducted for safety reasons (participant experiences a suspected Grade ≥ 3 IRR/CRS, or Grade ≥ 3 hypersensitivity reaction, or RO7300490-related Grade ≥ 2 AE leading to treatment interruption/discontinuation or delay), PK, ADA, and PD samples for cytokines and receptor occupancy will be collected. Of note, for participants who transferred from the imaging sub-study, only PK/ADA samples and plasma sample for cytokines (safety) will be collected in such instance. The PK/ADA/PD samples should be taken as soon as possible (i.e., ideally at the time of the development of such an event or, if not feasible, at the earliest possible convenience). If unscheduled PK/ADA/PD sampling time points fall during overnight hours and staff is not available for collecting/processing samples, collection can be delayed until the following morning. Every attempt should be made to collect the samples at the earliest possible convenience. If PK/ADA/PD sample collection is delayed until the following morning, it is critical that the actual PK/ADA/PD sampling collection time and date be documented in the eCRF.
- f) For all participants in Part 1 and Part 2, [REDACTED] which demonstrates favorable safety and preliminary anti-tumor activity or favorable PK/PD properties of RO7300490, collection of fresh tumor biopsies (at screening and on-treatment) and archival tumor sample (when available) is mandatory. On-treatment biopsy has to be collected on C3D3 (48h post EOI \pm 6h). If the participant discontinues treatment before the scheduled on-treatment biopsy time point, a biopsy should be collected at the time of treatment discontinuation. Additional biopsy at time of partial response (PR), stable disease (SD), progressive disease or any other time point of interest based on the participant's course of disease may be taken after discussion between the Investigator and the Sponsor, and upon participant consent.
- g) Blood for RBR may also be collected on the first dosing day (C1D1) prior to dosing.

2. **INTRODUCTION**

RO7300490 is a second generation, bi-specific fibroblast activation protein- α (FAP)-targeted CD40 agonist, humanized, immunoglobulin (Ig)G1-based monoclonal antibody (mAb), whose agonistic activity is strictly dependent on FAP cross-linking.

This entry-into human (EIH), Phase I study aims to establish the safety, tolerability, pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of RO7300490 (alone or in combination with atezolizumab) and to evaluate its anti-tumor activity in patients with advanced and/or metastatic solid tumors.

2.1 **STUDY RATIONALE**

The co-stimulatory receptor CD40, a member of the tumor necrosis factor (TNF) receptor superfamily, is expressed on antigen-presenting cells (APCs; dendritic cells [DCs], B cells, monocytes), endothelial cells, platelets, epithelial cells, and many human tumor cells. Therapeutic targeting of CD40 by agonistic mAb aims to activate CD40+ APCs and thereby boost tumor-specific cytotoxic T cell responses. The effective priming of CD8+ T cells strongly depends on the maturation of DCs, which is physiologically triggered via the binding of CD40 on DCs by CD40 ligand (CD40L) expressed on antigen-stimulated CD4+ T helper cells and can be reproduced by agonist CD40 antibodies ([Elgueta et al. 2009](#), [Vonderheide et al. 2007](#), [Vonderheide et al. 2020](#)).

FAP is predominantly expressed by a subset of cancer-associated fibroblasts in the tumor stroma of most epithelial malignancies (e.g., pancreatic cancer, breast cancer, non-small cell lung cancer [NSCLC]) and has a restricted expression on normal tissues ([Brennen et al. 2012](#)). RO7300490, a FAP-targeted agonistic CD40 antibody (FAP-CD40), specifically activates APCs via CD40 when it is cross-linked by ██████ cells, mainly in the tumor.

It is well known that cancers evolve immune escape mechanisms within the tumor microenvironment, in order to block immune surveillance by T cells ([Thommen and Schumacher 2018](#)). One of these involves the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint signaling pathway. Expression of PD-L1 is an adaptive response of tumor cells to interferon (IFN)- γ produced by activated T cells, which promotes in turn T cell suppression via checkpoint inhibition ([Wilke et al. 2011](#)). This negative feedback loop can be reverted by blocking PD-L1 from binding its receptor through atezolizumab (Tecentriq®), a PD-L1 blocking mAb. Previous studies combining conventional CD40 agonist selicrelumab (RO7009789; developed by the Sponsor) with atezolizumab have shown that this combination is safe and well tolerated (Study BP29392). Moreover, blockade of PD-L1 or PD-1 is not expected to stimulate de novo immune responses but rather to enhance ongoing immune responses against tumor antigens, because this axis is mostly implicated in the effector phase and not during priming of the cellular immune response ([Merelli et al. 2014](#)).

Similar to the untargeted CD40 agonist selicrelumab, RO7300490 has the potential to be a combination partner for multiple anti-cancer agents, including atezolizumab, to augment the immune response within the tumor, eventually resulting in improved clinical outcomes.

The rationale for the study design is provided in Section [4.2](#).

2.2 BACKGROUND

In the past two decades, cancer immunotherapy (CIT) has paved the way to improved treatment modalities for several cancer indications. However, despite the progress made, more is needed, largely because of the complex interplay of multiple dysregulated immune processes within the tumor environment. RO7300490 is being developed to overcome the narrow therapeutic index of non-targeted agonistic CD40 mAbs and achieve stronger activation of antigen-presenting cells (APCs) within the tumor microenvironment of [REDACTED] solid tumors while reducing off-target peripheral effects. RO7300490 is expected to show a safe profile and contribute as a valuable combination partner for the treatment of patients with a wide range of [REDACTED] solid tumors.

A detailed description of the background of disease, current therapies, unmet medical needs, as well as a description of chemistry, pharmacology, efficacy, and safety of RO7300490 is provided in the [Investigator's Brochure](#).

2.3 BENEFIT/RISK ASSESSMENT

To date, only a minority of patients benefit from CIT and responses are mostly of limited duration. Inefficient antigen presentation and T cell priming in the intra-tumoral microenvironment is hypothesized to limit the efficacy of current CIT such as checkpoint inhibitors or cancer vaccines. Activation of CD40 expressed on APCs with agonistic antibodies has been identified as a promising approach to enhance T cell priming and antigen presentation, which may lead to higher response rates, and deeper and longer lasting responses.

Several untargeted CD40 agonistic antibodies, including selicrelumab, have been extensively profiled in clinical development programs, as intravenous (IV) and/or subcutaneous drug compounds as single agent or in combination with other anti-cancer agents or DC-growth factors ([Sanborn et al. 2019](#), [Vonderheide 2020](#)). Overall, they demonstrated limited clinical activity and early dose-limiting toxicities (DLTs) likely related to peripheral CD40 activation that precluded their dose-escalation to reach pharmacologically relevant exposures within the tumor. Recently, the tumor targeted anti-mesothelin (MSLN)-CD40 agonist IgG1 bispecific antibody ABBV-428, whose pharmacological activity depends on MSLN-CD40 cross-linking in tumor, showed a much better clinical safety profile compared with the untargeted CD40 agonist mAb. It was very well tolerated in patients with cancer (up to 3.6 mg/kg IV), with no apparent toxicities related to peripheral CD40 activation ([Luke et al. 2019](#)).

The FAP-targeted CD40 mAb RO7300490 is designed to enable higher tumor exposure and longer tumor retention compared with that of untargeted CD40 antibodies, while minimizing systemic side effects, due to peripheral target activation.

Study WP42627 is an *ongoing* EIH study; therefore, *detailed* clinical efficacy and the actual risks of RO7300490 in patients with advanced/metastatic solid tumors are unknown. RO7300490 demonstrated a remarkably improved safety profile compared with that of non-targeted CD40 agonist selicrelumab in non-human primates ([RO7300490 Investigator's Brochure](#) and Section 4.3.1). Based on currently available nonclinical data, RO7300490 is not anticipated to trigger a severe systemic immune response as a single agent, because it requires FAP target-dependent cross-linking for activity and has been engineered to abrogate FcγR-binding. In addition, the FAP binding moiety of RO7300490 is expected to result in accumulation/retention of the compound in the tumor microenvironment. Thus, the abrogated FcγR-binding along with the FAP-targeted technology of RO7300490 is expected to minimize the risk for systemic or off-tumor-on-target stimulation of immune effector cells and to contribute to accumulation in the local tumor microenvironment, compared with untargeted CD40 agonists.

One potential development risk is posed by the presence of pre-existing anti-drug antibodies (pADA) [REDACTED]

The presence of pADA might trigger events ranging from none to life-threatening reactions after the first administration of RO7300490 ([Xue et al. 2017](#), [Gorovits et al. 2016](#)). Potential safety risks associated with pADA include acute toxicity, such as infusion-related reactions/cytokine release syndrome (IRR/CRS), and delayed toxicity due to immune complex formation, such as vasculitis or glomerulonephritis. [REDACTED]

[REDACTED] The clinical relevance of pADA cannot be predicted from animal data. Therefore, whether pADA will present a real risk for RO7300490 development is currently unknown and will be closely monitored.

Safety measures based on the potential risks identified during pre-clinical studies of RO7300490 and in the course of the past clinical experience with selicrelumab, a CD40 agonist, are implemented in this study. These include a careful definition of the eligibility criteria, a model-based approach with built-in safety constraints to guide dose-escalation, enrollment staggering, and frequent and extensive safety assessments to allow early diagnosis and treatment of treatment-emergent toxicity. Rules for treatment interruption/discontinuation and recommendations for the management of specific adverse events (AEs) are provided in this protocol.

RO7300490 has the potential to be a combination partner for multiple anti-cancer agents, including atezolizumab. Therapeutic blockade of PD-L1 binding by atezolizumab enhances the quality and magnitude of tumor-specific T cell responses ([Fehrenbacher et al. 2016](#), [Rosenberg et al. 2016](#)). Combination of RO7300490 and atezolizumab may synergistically activate immune response in the tumor, resulting in improved and durable responses.

IRRs/CRS, immune-mediated adverse events, thrombocytopenia, hemophagocytic lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS) represent potential overlapping toxicities when RO7300490 is combined with atezolizumab. The clinical experience with selicrelumab and atezolizumab informed risk mitigation strategies that include management guidelines for potential overlapping toxicities. Participants will be monitored closely to ensure early diagnosis and treatment of potential overlapping toxicities.

The non-clinical data set for RO7300490 ([RO7300490 Investigator's Brochure](#)), the respective safety data from completed clinical studies with non-targeted CD40 agonist selicrelumab (single agent or in combination with atezolizumab [Study BP29392]), the measures in place to mitigate and manage potential toxicities, *and currently available data from Part 1 of this study* provide an acceptable benefit-risk balance for the clinical investigation of RO7300490 in patients with advanced/metastatic solid tumors for whom no effective standard therapy exists.

More detailed information about the known and expected benefits, potential risks, and reasonably expected AEs of RO7300490 is provided in the [RO7300490 Investigator's Brochure](#). Detailed information about the known and expected benefits and potential and identified risks of atezolizumab is provided in the most current version of the [atezolizumab Investigator's Brochure](#).

2.3.1 COVID-19 Benefit/Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, participants with comorbidities, including those with advanced solid tumors, are a more vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses ([Dai et al. 2020](#), [Shah et al. 2020](#), [Yang et al. 2020](#), [Robilotti et al. 2020](#)). It is, however, unclear whether or how cancer therapies such as chemotherapy, targeted therapy, or immunotherapy affect the incidence or severity of *SARS-CoV-2 infection*. It is not known whether RO7300490 will increase the risk of infection with SARS-CoV-2. Severe *SARS-CoV-2 infection* is associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2 and IFN- γ ([Merad and Martin 2020](#)). RO7300490 is an immunostimulatory agent that has a potential risk of CRS, and *atezolizumab is a modulator of the host immune response, which may result in immunopathology or dysregulated immune system defenses upon acute infection. While it is not known, there may be a potential for an increased risk of an enhanced*

inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving RO7300490 and/or atezolizumab. At this time, there is insufficient evidence for causal association between RO7300490 or atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

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

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immunotherapy), with the understanding that there are limited safety and efficacy data in such patients ([NCCN 2021](#)). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For participants enrolling in this study and receiving RO7300490 and/or atezolizumab treatment, a decision to administer the vaccine should be made on an individual basis by the Investigator in consultation with the participant. Please refer to Section [6.5.1](#) for further recommendations.

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

SITC and NCCN recommendations along with institutional guidelines should be used by the Investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (Section [6.5](#)).

Potential Lymphadenopathy after COVID-19 Vaccination

Vaccination is an established but uncommon cause of ipsilateral transient lymphadenopathy; this has been described with several currently available COVID-19 vaccinations ([Tu et al. 2021](#)).

When interpreting tumor response on imaging, Investigators are encouraged to take the timing of the vaccination and the side of the vaccination into consideration. Consider performing follow-up assessments as per Investigators' clinical judgement and published guidance can aid in identifying appropriate approaches to distinguishing vaccine-induced lymphadenopathy from malignancy (Lehman et al. 2021). The schedule of tumor response assessments should not be a consideration when scheduling the vaccination. Vice versa, the schedule for tumor response assessments must continue to be followed, regardless of when the COVID-19 vaccine was administered.

When vaccines are administered, side effects—including axillary swelling—possibly attributable to vaccination should be managed at the discretion of the Investigator. The Medical Monitor should be contacted if there are any questions or concerns regarding characterization and management of ipsilateral lymphadenopathy.

3. **OBJECTIVES AND ENDPOINTS**

The objectives and corresponding endpoints are provided in [Table 5](#).

Table 5 Objectives and Endpoints

• Objectives	• Endpoints
• Primary	
• To evaluate the safety and tolerability profile of RO7300490 as a single agent (Part 1) or in combination with atezolizumab (Part 2)	• Incidence, nature, and severity of adverse events (AEs) graded according the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for cytokine release syndrome (CRS)
• To determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of RO7300490 as a single agent (Part 1) or in combination with atezolizumab (Part 2)	• Nature and frequency of dose-limiting toxicities (DLTs)
• To assess the anti-tumor activity of RO7300490 in combination with atezolizumab [REDACTED] Part 3)	• Objective response rate (ORR) According to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

• Objectives	• Endpoints
• Secondary	
<ul style="list-style-type: none"> To characterize the pharmacokinetics (PK) profile of RO7300490 as a single agent (Part 1) and in combination with atezolizumab (Parts 2 and 3) 	<ul style="list-style-type: none"> PK profiles and parameters of RO7300490 after intravenous (IV) administration (e.g. area under the curve [AUC], minimum concentration [C_{min}], maximum concentration [C_{max}], clearance [CL], volume of distribution at steady-state conditions [V_{ss}])
<ul style="list-style-type: none"> To evaluate the anti-RO7300490 immune response to RO7300490 treatment (Parts 1, 2, and 3) 	<ul style="list-style-type: none"> Incidence and titer of RO7300490 anti-drug antibodies (ADA) during the study relative to prevalence of pre-existing ADA (pADA) at baseline
<ul style="list-style-type: none"> To assess the anti-tumor activity of RO7300490 alone (Part 1) and in combination with atezolizumab (Part 2) 	<ul style="list-style-type: none"> ORR Disease control rate (DCR) Duration of response (DoR) Progression-free survival (PFS; on-treatment) <p>All according to RECIST v1.1 by Investigator's assessment</p>
<ul style="list-style-type: none"> To assess the anti-tumor activity of RO7300490 in combination with atezolizumab [REDACTED] [REDACTED] Part 3) 	<ul style="list-style-type: none"> DCR DoR PFS <p>All according to RECIST v1.1 by Investigator's assessment</p>
<ul style="list-style-type: none"> To evaluate the safety and tolerability of RO7300490 in combination with atezolizumab [REDACTED] [REDACTED] Part 3) 	<ul style="list-style-type: none"> Incidence, nature, and severity of AEs graded according to the NCI CTCAE v5.0 and according to ASTCT Consensus Grading for CRS
<ul style="list-style-type: none"> To evaluate the potential effects of RO7300490 ADA and pADA 	<ul style="list-style-type: none"> Analysis of relationship between ADA/pADA incidence and safety, PK, or pharmacodynamic (PD) endpoints
• Exploratory	
<ul style="list-style-type: none"> To evaluate potential relationships between RO7300490 exposure and PD biomarkers 	<ul style="list-style-type: none"> Relationship between PK parameters for RO7300490 and PD biomarkers, including but not limited to CD40 receptor occupancy on B cells and markers of immune cell subset function or activation status.
<ul style="list-style-type: none"> To evaluate PD biomarkers from blood or paired biopsies to investigate the MoA of RO7300490 and its relationship to RO7300490 dose 	<ul style="list-style-type: none"> Biomarker assessments in peripheral blood such as lymphocyte counts, CD40 receptor occupancy, or soluble markers (e.g., chemokines, cytokines)

• Objectives	• Endpoints
	<ul style="list-style-type: none"> Biomarker assessments in paired tumor tissue such as APC, or T cell subset function, or activation status
<ul style="list-style-type: none"> To evaluate biomarkers in peripheral blood and tumor tissue for response prediction 	<ul style="list-style-type: none"> Biomarker assessments in peripheral blood such as lymphocyte counts, CD40 receptor occupancy, or soluble markers (e.g., chemokines, cytokines) [REDACTED]
<ul style="list-style-type: none"> To evaluate the potential effect of selected covariates on RO7300490 exposure 	<ul style="list-style-type: none"> Relationship between selected covariates and PK parameters for RO7300490 (population PK [popPK])
<ul style="list-style-type: none"> To make a preliminary assessment of the efficacy of tocilizumab in ameliorating the symptoms of severe CRS after treatment with RO7300490 	<ul style="list-style-type: none"> Outcome of severe CRS following the administration of tocilizumab
<ul style="list-style-type: none"> To characterize treatment-induced PD effects of RO7300490 in the tumor microenvironment 	<ul style="list-style-type: none"> Changes from baseline in immune cell subset counts, function, or activation status
<ul style="list-style-type: none"> To explore the degree of target binding of RO7300490 	<ul style="list-style-type: none"> CD40 receptor occupancy on B cells
<ul style="list-style-type: none"> To further assess the anti-tumor activity of RO7300490 alone (Part 1) and in combination with atezolizumab (Part 2 and 3) 	<ul style="list-style-type: none"> ORR DCR DoR PFS <p>All according to immuneRECIST (iRECIST)</p> <ul style="list-style-type: none"> Overall Survival (OS) if data are mature

4. **STUDY DESIGN**

4.1 **OVERALL DESIGN**

Study Design

This is an EIH, open-label, multicenter, multiple-ascending dose-escalation and expansion, Phase I clinical study of RO7300490 as single agent or in combination with atezolizumab.

The study consists of three parts:

- Part 1: dose-escalation of RO7300490 as a single agent.

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- Part 2: dose-escalation of RO7300490 in combination with atezolizumab.
- Part 3: dose-expansion of RO7300490 in combination with atezolizumab in selected cancer types. [REDACTED] and implemented with an amendment to the protocol.

Part 2 will start after RO7300490 has demonstrated acceptable safety and tolerability, and favorable PK/PD properties as single agent in Part 1, and once evidence of efficacy and/or MoA of RO7300490 has been established. In the event that this evidence is available before Part 1 is completed (RO7300490 maximum tolerated dose [MTD] or recommended dose for expansion [RDE] determined), Part 1 and Part 2 may run in parallel, if concurrent enrollment is supported by safety and PK/PD data.

Part 3 will be initiated after the MTD or RDE of RO7300490 in combination with atezolizumab (Part 2) is defined.

At least 3 evaluable participants will be enrolled in each cohort during the dose-escalation in Parts 1 and 2. If deemed necessary to further characterize the safety, PK, and/or PD profile of RO7300490, additional participants may be enrolled after agreement between Investigators and the Sponsor at the doses already tested or in additional cohorts at doses that have not been explored for the determination of the MTD.

It is planned to mandate tumor biopsies (at screening and on-treatment) and archival tumor samples collection (if available) for all participants in Part 1 and Part 2, in order to investigate RO7300490 MoA. [REDACTED]

[REDACTED] Tumor tissue is collected in order to characterize treatment-induced PD effects of RO7300490, alone or in combination, in the tumor microenvironment and to validate PK/PD model assumptions.

For participants enrolling in Part 3, [REDACTED]

The assignment of participants to a cohort will be randomized when several cohorts (e.g., dose-escalation cohorts [Parts 1 and 2]) enroll simultaneously (Section 6.3).

Treatment Groups and Duration

Part 1: RO7300490 single agent dose-escalation

[REDACTED]

For participants on this treatment schedule, the cycle length is 14 days. If justified by emerging safety, PK and PD, and efficacy data, the Sponsor (in agreement with Investigators) may modify the drug administration frequency to every 3 weeks (Q3W). For participants on this modified treatment schedule, the cycle length is 21 days.

Intra-participant dose-escalation

To minimize the exposure of participants to suboptimal doses of RO7300490, intra-participant dose-escalation may be permitted after the second on-treatment tumor assessment has been performed, as indicated in the SoAs (Section 1.3). If there are no major safety concerns, a participant may receive a higher RO7300490 dose, up to a dose that has been considered safe within the participant's dosing schedule, and which is at least one dose level below the highest current evaluated dose in Part 1, or up to the MTD, if reached. Once the participant has received the higher dose without experiencing an AE that meets the definition of a DLT or that requires post-administration hospitalization, he/she may be eligible for further escalations, as higher cleared dose levels become available.

All intra-participant dose-escalation decisions will be made by the Sponsor in consultation with the Investigator.

[REDACTED]

[REDACTED]

[REDACTED]

Part 2: RO7300490 dose-escalation in combination with atezolizumab

Participants will receive escalating doses of RO7300490 in combination with a fixed dose of atezolizumab IV. The starting dose of RO7300490 will be determined based on the evaluation of the emerging data from Part 1 that is available at the time of starting Part 2. The starting dose in Part 2 will be initiated at least one dose level below the highest dose already cleared during the dose-escalation in Part 1.

[REDACTED]

[REDACTED] For participants on this treatment schedule, the cycle length is 14 days. If justified by emerging safety, PK, PD, and efficacy data, the Sponsor may modify the frequency of RO7300490 administration to Q3W. In that case, atezolizumab will be administered Q3W at a dose of 1200 mg. For participants on this modified treatment schedule, the cycle length is 21 days.

Part 3: RO7300490 in combination with atezolizumab [REDACTED]
[REDACTED] and implemented with an amendment)—
dose-expansion in tumor-specific cohorts

[REDACTED]

Imaging sub-study: In addition to the main study (Parts 1, 2, and 3), an immuno-positron emission tomography (PET) imaging sub-study is planned to assess the tumor accumulation and tissue bio-distribution of RO7300490 using [⁸⁹Zr]-labeled RO7300490 as a radiotracer. This imaging sub-study will be initiated soon after the main study WP42627 has started and will only be conducted in the European Union (EU).

Participants who have completed the imaging sub-study will be eligible to receive RO7300490 single agent in Part 1 of the WP42627 main study from Cycle 2 Day 1 (C2D1) onwards. A direct move from the imaging sub-study to Part 2 may also be considered, provided Part 2 is already enrolling and the RO7300490/atezolizumab combination dose under consideration has been assessed as safe. Decision to transfer to the main study will be made by the Sponsor in consultation with the Investigator.

An overview of the study design is provided in Section [1.2](#).

4.1.1 Length of the Study

The maximum duration in the study for each participant will be 27 months, divided as follows:

- Screening: Days -28 to -1.
- Treatment Period: Maximum duration of 24 months from C1D1 until the last dose of study treatment (may be modified by the Sponsor if supported by emerging data).
- Safety follow-up: 60 days (\pm 7 days) after the last dose of study treatment.
- Survival follow-up: 3-monthly (\pm 14 days) after the last dose of study treatment (period not considered for the calculation of the maximum study duration).

4.1.2 Dose-Escalation Decision Criteria

A Bayesian model-based approach, i.e., the modified continual reassessment method (mCRM) with escalation with overdose control (EWOC) design ([Neuenschwander et al. 2008](#)), will guide the dose-escalation of RO7300490 for Part 1 and Part 2 of the study and will be based on the occurrence of DLTs (Section [4.1.3](#)).

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. The dose-toxicity relationship is described by a 2-parameter logistic regression model, which is continuously updated as additional participant information becomes available. The MTD is defined as the dose with the highest probability that the DLT rate is within the target of 20% to 35%, and a relatively low probability (< 25%) that the DLT rate is above 35%.

For both Parts 1 and 2 of the study, at least three DLT-evaluable participants will be enrolled at each dose level. All 3 participants must finish the DLT assessment window (see [Table 8](#)) to be considered in the continual reassessment method (CRM) analyses. The first participant at each dose level must have completed at least 3 days from the first administration of study treatment without a DLT before the next participant can be treated simultaneously at this dose level. For enrollment of each subsequent participant, there should be at least 1 day in between. However, if any participant experiences a DLT within the first 3 days after the first administration of study treatment, the treatment of the next participant will be staggered by at least 3 days.

Once there are three DLT-evaluable participants in a cohort, the model will be updated with the treatment outcome (i.e., occurrence of DLT or not) and a new estimate of the MTD will be derived (Section [4.1.3.1](#) and [Table 6](#)). A participant who has experienced a DLT event but has not finished the DLT-assessment window is considered DLT-evaluable and will be included in the current dose analysis. Those participants who have not experienced a DLT event and have not completed their DLT window will be influencing the dose-escalation decision in the next appropriate cohort, once they complete their DLT window; this includes participants in Part 1 extension cohorts. Participants who do not complete the DLT window for reasons other than safety (e.g. including but not limited to: progressive disease, death, withdrawal from study) are not considered DLT-evaluable and will not be included in any dose-escalation analyses.

Enrollment into a next dose cohort will only start after the Sponsor and the Investigators have jointly decided on the next dose-escalation level, following the review of all relevant safety information (and any other available data that may assist the dose-escalation decision process) from the current and previous cohorts collected until the time point of dose evaluation, and taking into account the EWOC recommendation (see the communication strategy in Section [4.1.5](#)). The Sponsor and the Investigators will be able to overrule the model recommendation based on safety concerns, if needed. At each dose-escalation step, the dose can be escalated, de-escalated, or further investigated by

expansion of the current dose-level cohort. The requirements for data review to support the dose-escalation decision, including the timing of data availability, data cleaning, timing of meetings between the Sponsor and the Investigators, and roles and responsibilities are documented in the Medical Data Review Plan/Dose-escalation Plan.

The design will continue as described, assigning participants to the MTD as estimated from all DLT data cumulatively, until one of the predefined stopping criteria is satisfied ([Appendix 6](#)). Once the MTD and/or RDE have been determined, all ongoing participants can switch to the MTD or RDE.

Built-in safety constraints are in place to prevent exposing participants to undue risk of toxicity. Given the favorable safety profile observed in nonclinical assessments [REDACTED] in cynomolgus monkeys (Section 4.3.1, [RO7300490 Investigator's Brochure](#)), in absence of a DLT, the maximum allowable increment will be 200% until 150 mg. [REDACTED] Thereafter, the maximum dose increment will be 100%. If one DLT occurs then a maximum increment of 50% will be allowed, and if 2 or more DLTs, a maximum increment of 33% will be allowed.

In a recent Food and Drug Administration (FDA) oncology review of first-in-human studies, a 3-fold (i.e., 200%) escalation has been assumed 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](#)). Thereafter, a more conservative 2-fold escalation (100%) increment is proposed to carefully characterize the safety and tolerability profile of RO7300490.

Details are provided in [Appendix 6](#). An example of a dose-escalation as recommended by the mCRM-EWOC design given the scenario of no DLTs is provided in [Table 6](#). For details, see [Appendix 6, Table 1](#) (Dose-escalation Mock Runs).

Table 6 RO7300490 Dose levels for Study Part 1 in Absence of DLT

Dose Level	Dose (mg)	Dose Increment if No DLT (%)	Next Dose if No DLT (mg)
1	16	200	48
2	48	192	140
3	140	100	280
4	280	96	550
5	550	100	1100
6	1100	36	1500
7	1500	0	1500

4.1.2.1 Part 1: RO7300490 Single Agent Dose-Escalation

The dose-escalation of RO7300490 in Part 1 will be guided by the mCRM-EWOC design to determine the MTD and/or RDE, by using primary safety variables (e.g., DLT). The prior distribution for the parameters of the DLT dose-response curve will be minimally informative and constructed based on the assumed not toxic and toxic doses (Figure 2,

[Appendix 6](#)). The initial dose of RO7300490 as single agent is set at 16 mg (as justified in Section [4.3](#)). At any time, dose-escalation may be paused or halted prior to the identification of MTD/RDE and upon sufficient characterization of the IMP in regards to safety, PK, and/or PD.

4.1.2.2 Part 2: RO7300490 Dose-Escalation in Combination with Atezolizumab

The dose-escalation of RO7300490 in Part 2 will be guided by the mCRM-EWOC design. The starting dose will be determined based on the evaluation of the total emerging PK, receptor occupancy, tumor bio-distribution (if available), and safety data from RO7300490 single agent that are available from Part 1 when starting Part 2. The starting dose in Part 2 will be initiated at least one dose level below the highest dose already cleared during the dose-escalation in Part 1. Based on emerging safety and available PK and/or PD data, the interval between initial administration of RO7300490 in combination with atezolizumab to the first participant and in subsequent participants within each dose level may be adjusted as deemed appropriate by the Investigators and the Sponsor. Dose-escalation may be paused or halted prior to the identification of the MTD/RDE for the combination treatment if sufficient characterization in regards to safety, PK, and/or PD is available. In case the MTD/RDE has not been reached in Part 1 (RO7300490 as single-agent), or if Part 1 dose-escalation is paused or halted prior to the identification of the MTD/RDE, Part 2 dose-escalation may go beyond the maximum safe dose tested in Part 1.

4.1.3 Dose-Limiting Toxicities

A DLT is defined as one of the toxicities described in [Table 7](#) related to RO7300490 or RO7300490 in combination with atezolizumab that occur during the DLT assessment window (see Section [4.1.3.1](#)) and it is not attributable to the underlying disease or an intercurrent illness.

For the assessment of DLTs, all AEs will be graded according to NCI CTCAE v5.0, except for CRS, which will be graded based on the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading criteria ([Lee et al. 2019](#); [Appendix 9](#)). DLTs will be treated according to clinical practice and the guidelines provided in Section [8.3.9](#) and [Appendix 10](#) and will be monitored through their resolution.

Toxicities fulfilling the DLT definition and considered related to study treatment, that occur outside of the DLT assessment window will be considered for the determination of the overall tolerability and safety profile of RO7300490 either alone (Part 1) or in combination with atezolizumab (Part 2), and may be used to inform dose decisions for future cohorts.

Table 7 Adverse Events Considered Dose-Limiting Toxicities

Toxicity	Dose-Limiting Toxicity Criteria
Hematological toxicities	<ul style="list-style-type: none"> Any Grade ≥ 3 hematologic AE not considered by the Investigator to be attributable to another clearly identifiable cause, with the following exceptions: <ul style="list-style-type: none"> Grade 3 or 4 lymphopenia that improves to Grade ≤ 1 within 7 days. Grade 3 or 4 neutropenia that is not accompanied by temperature elevation (oral or tympanic temperature of $\geq 38^{\circ}\text{C}$) and lasting 1 week or 3 days, respectively. Grade 3 thrombocytopenia, that improves to Grade ≤ 2 (or to $\geq 80\%$ of the baseline value, whichever is lower) within 7 days without platelet transfusion and is not associated with bleeding that is considered clinically significant by the Investigator. Grade 3 anemia without hemolysis.
Non-hematological toxicities	<ul style="list-style-type: none"> Any Grade ≥ 3 non-hematologic AE not considered by the Investigator to be attributable to another clearly identifiable cause, with the following exceptions: <ul style="list-style-type: none"> Grade 3 nausea, vomiting or diarrhea including their clinical sequelae (e.g., fluid loss with subsequent dehydration, electrolyte loss [sodium, potassium, magnesium, chloride]) that resolve to Grade ≤ 1 within 72 hours. Fever $> 40^{\circ}\text{C}$ (i.e., Grade 3) that occurs within 48 hours of RO7300490 administration and resolves within 48 hours to $< 40^{\circ}\text{C}$ (Grade ≤ 2) and fully resolves within 7 days. Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days. Grade ≥ 3 laboratory abnormalities that are asymptomatic and deemed by the Investigator not to be clinically significant. Alopecia (any grade). Grade 3 arthralgia that can be adequately managed with supportive care or which resolves to Grade ≤ 2 within 7 days. Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor that starts within 24 hours of infusion and lasts less than 3 days and does not require intervention aimed at preventing compression of adjacent organs. Grade 3 neuropathy if the participant began therapy with Grade 2 neuropathy at baseline. Grade 3 constipation. Grade 3 hypophosphatemia resolved within 7 days. Grade 3 IRRs that resolve within 24 hours to \leq Grade 1.
Liver function tests (LFT)	<ul style="list-style-type: none"> Grade ≥ 3 AST or ALT. Grade 3 hyperbilirubinemia lasting for > 48 hours or Grade 4 hyperbilirubinemia. AST or ALT $\geq 3 \times$ the upper limit of normal (ULN) with total bilirubin $> 2 \times$ ULN.

Toxicity	Dose-Limiting Toxicity Criteria
	<p>Exceptions:</p> <ul style="list-style-type: none"> - In participants with liver lesions, Grade 3 transient increase of <i>total</i> bilirubin, transaminases (AST/ALT) and/or gamma-glutamyl transferase (GGT) that starts within 24 hours of infusion and recovers to Grade ≤ 1 or baseline within 7 days. - AST or ALT $\geq 3 \times$ ULN and total bilirubin $> 2 \times$ ULN (where not a single value for bilirubin exceeds Grade 3) occurring in the context of Grade ≤ 2 CRS (as defined by the criteria established by Lee et al. 2019; see Appendix 9) or lasting < 3 days will not be considered as a DLT. Under this condition, an unscheduled test must be performed to confirm the duration of the AST or ALT elevation. - Any Grade ≥ 3 AST or ALT elevation occurring in the context of Grade ≤ 2 CRS or lasting < 3 days will not be considered as a DLT. Under this condition, unscheduled test must be performed to confirm the duration of the AST or ALT elevation.
Dose delays	<ul style="list-style-type: none"> • Inability to complete 2 administrations of RO7300490 (Part 1) or 2 administrations of RO7300490 and atezolizumab (Part 2) in the DLT assessment window because of lack of recovery to a Grade ≤ 1 toxicity or lack of recovery to baseline that is related to the study treatment. Dosing may be delayed by up to 14 days to monitor for toxicity, and to assess the relatedness of an observed toxicity to the study treatment.
Other	<ul style="list-style-type: none"> • Any other study treatment-related toxicity considered significant enough to qualify as a DLT in the opinion of the Investigator and after discussion with the Sponsor.

AE = Adverse event, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, CRS = Cytokine release syndrome, DLT = Dose-limiting toxicity, IRR = Infusion-related reactions, ULN = Upper limit of normal

4.1.3.1 DLT Assessment Window

The DLT assessment window applies to participants enrolled in the dose-escalation cohorts in Part 1 or in Part 2 of the study, and to participants enrolled in the Part 1 extension cohorts. It will not apply to participants who transfer from the imaging sub-study.

In Part 1, the DLT assessment window starts on C1D1 (first administration of RO7300490) and ends one week after the second dose is administered (i.e., C2D7). In Part 2, the DLT assessment window starts on C1D1 (first administration of study treatment: atezolizumab and RO7300490) and ends one week after the second dose of both drugs has been administered (i.e., C2D7).

If the second dose of study treatment (C2D1) must be delayed by 1 day for non-safety reasons (such as a bank holiday, administrative impediment), the DLT period should be adjusted accordingly to cover one week post dosing ([Table 8](#)).

Table 8 DLT-Assessment Window Based on Treatment Schedule

Treatment schedule	DLT observation period
Q2W	21 days from C1D1 to C2D7 (+1 day if C2D1 is delayed)
Q3W (if explored)	28 days from C1D1 to C2D7 (+1 day if C2D1 is delayed)

C = Cycle, D = Day, DLT = Dose-limiting toxicity, Q2W = Every 2 weeks, Q3W = Every 3 weeks.

In the event that the second dose (C2D1) is delayed (as per toxicity category: “Dose delays” in [Table 7](#)), the DLT assessment window should be adjusted accordingly to include C2D7. Since the maximum dose delay is 14 days, the DLT assessment window may be adjusted up to a maximum of 35 (Q2W) or 42 (Q3W) days.

Replacement of Participants

The following participants enrolled in the dose-escalation cohorts in Part 1 or in Part 2 of the study will not be considered as evaluable for DLT and will be replaced:

- Participants who discontinue from the study before the end of the DLT assessment window for reasons other than safety (e.g. including but not limited to progressive disease, death, withdrawal from study).
- Participants who receive palliative radiotherapy during the DLT assessment window.

Participants enrolled in the Part 1 extension cohorts who fail to be DLT-evaluable will not need to be replaced.

4.1.4 Stopping Rules Criteria

The dose-escalation in Part 1 and Part 2 will be halted if any of the stopping criteria listed in [Appendix 6](#) apply. In accordance with clinical judgment and after discussion and documented agreement by the Sponsor and the Investigators, dose-escalation may continue beyond stopping criteria.

4.1.5 Communication Strategy

The participants may be enrolled once eligibility is confirmed in the Interactive Response Technology (IRT) system. This will ensure that the Sponsor is notified of every participant prior to the administration of the study treatment.

Upon completion of the first study treatment administration (i.e., RO7300490 alone or in combination with atezolizumab), the Investigator 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 to RO7300490 as a single agent or in combination with atezolizumab. The Investigator should communicate this information by email and/or telephone, as soon as reasonably possible and within one business day.

In addition, in the event of a DLT, the Investigator will contact the Sponsor immediately to discuss participant status and action taken and/or to be taken.

Investigators must ensure that data from the participants enrolled at their sites are reported in the electronic case report form (eCRF) in a timely manner, so that they are available to the Sponsor for review and discussion. In addition, once the DLT assessment window is complete, the Investigators must confirm the participant status by providing a brief summary about safety and treatment tolerability to the Sponsor.

Before a new dose cohort is opened, the Sponsor will organize a teleconference with the Investigators to discuss the safety and tolerability of the study treatment and to determine the dose for the next cohort. If the teleconference occurs prior to the end of the DLT observation period, the next cohort will only start after the Investigator provided a final participant status and the Sponsor confirmed the next dose level. RO7300490 dose decisions will be taken independently for the dose-escalation of RO7300490 as a single agent or in combination, but the corresponding teleconferences might be jointly held if timing allows.

During each teleconference, toxicities ([Appendix 2](#)) will be discussed along with the available PK, anti-drug antibody (ADA), and PD data, in addition to safety laboratory results and any other available data that may assist the dose-escalation decision process (see the Dose-Escalation Plan for further details). Dose-escalation will only proceed to the next dose level if the Sponsor and the Investigators are satisfied with the safety profile of the previous cohort and agree to move to the next dose level. The discussion will be documented in writing and both the Sponsor and Investigators will approve the dose decisions made during these meetings to confirm their agreement.

In addition to these communications, the Sponsor and the Investigators will be in regular contact throughout the study by email/telephone, as per normal interactions during the conduct of a clinical study, and the Sponsor will arrange regular teleconferences and meetings to discuss the study status. The Sponsor will be available 24 hours a day to discuss any medical or study-related issues that may arise during the conduct of this study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section [2.1](#).

4.2.1 Rationale for Study Population

Parts 1 and 2 (dose-escalation) of this study will enroll participants diagnosed with advanced and/or metastatic solid tumors who progressed on previous cancer therapy/ies or for whom no effective standard therapy exists, *irrespective of the number and type of previous therapy lines*.

RO7300490 is a FAP-targeted CD40 agonist, which requires FAP cross-linking to be active. Human solid tumors, including epithelial malignancies, are characterized by the expression of FAP at varying degrees and extend within the tumor microenvironment. It is estimated that FAP is upregulated in > 90% of carcinomas, particularly on the cell

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surface of tumor stromal fibroblasts and activated cancer-associated fibroblasts (RO7300490 Investigator's Brochure). [REDACTED]

[REDACTED] These indications include NSCLC, small-cell lung cancer (SCLC), triple-negative breast cancer (TNBC), cutaneous melanoma, *urothelial cancer (including renal pelvis, ureters, urinary bladder and urethra)*, mesothelioma, hepatocellular carcinoma (HCC), head and neck squamous cell carcinoma (HNSCC), esophageal squamous cell carcinoma (ESCC) and cervical squamous cell carcinoma (SCC).

Activation of APCs via CD40 within the tumor environment is thought to promote cytotoxic T cell mobilization and activation. [REDACTED]

[REDACTED] Therefore, the participants are likely to benefit from RO7300490 treatment, in particular when combined with a checkpoint inhibitor.

Part 3 (expansion cohorts) will enroll participants with selected [REDACTED] solid tumors, based on the emerging safety and PK/PD data from the dose-escalation cohorts. In addition, [REDACTED]

[REDACTED] The patient selection strategy and treatment regimen will be defined in an amendment to the protocol.

4.2.2 Rationale for Biomarker Assessments

RO7300490 is designed to be active in tumor-associated stromal tissue expressing FAP. It targets CD40-expressing APCs (myeloid DCs, macrophages, and B cells), which co-localize with FAP-expressing stromal compartments adjacent to tumor nests. Efficient APC activation will result in upregulation of activation markers and secretion of pro-inflammatory chemokines/chemokine ligands and cytokines. DCs may also mature and migrate to lymph nodes where they will present tumor antigens to T cells, ultimately resulting in increased infiltration of activated CD8+ T cells into the tumor microenvironment.

The biomarker analysis will focus on demonstrating key aspects of RO7300490 mode of action (MoA) within the tumor tissue and addressing questions related to systemic RO7300490 effects in peripheral blood. Additional biomarkers may be measured if initial data lead to a strong scientific rationale for these measurements.

Peripheral Blood and Plasma Markers

RO7300490 can bind to CD40 present outside of the tumor tissue. CD40 is highly expressed by most or all circulating B cells and to a lesser degree by monocytes. Circulating B cells are thus expected to act as a significant sink for RO7300490, which may need to be saturated before the study drug can reach the target tumor tissue. The amount of RO7300490 bound to peripheral B cells will be determined (herein receptor occupancy) and correlated with PK parameters and imaging data to improve estimates at which dose specific tumor accumulation of RO7300490 might occur.

Historically, circulating B cells have represented a primary PD biomarker for CD40-activating treatments. Several conventional CD40 agonistic drugs showed transient peripheral B cell activation, coupled with a transient decrease of B cell counts ([Machiels et al. 2020](#)). Although unlikely, in light of its targeted MoA, it cannot be excluded that systemic B cell activation might occur at high doses of RO7300490. Therefore, the numbers of lymphocyte subsets, including but not limited to B cells, T cells and natural killer (NK) cells, will be assessed during study treatment. [REDACTED] [REDACTED] In addition, it might inform on potential safety issues, indicating possible systemic effects rather than tumor-targeted activation at any RO7300490 dose tested.

Soluble CD25 and a panel of immune cell relevant cytokines will also be assessed in plasma, in order to evaluate downstream intra-tumoral PD events or advance the understanding of potential AEs related to study treatment.

Tumor Tissue Investigations

The exploratory objective of tumor tissue PD biomarker analysis is to investigate the MoA of RO7300490. This will include measurement of markers associated with APC activation such as surface receptors involved in T cell activation and pro-inflammatory chemokines/chemokine ligands, or cytokines. In addition, more downstream PD biomarkers such as CD8+ T cell infiltration or functional markers of CD8+ T cells will be investigated. [REDACTED] [REDACTED]

RO7300490 activity in tumor is expected to correlate with the expression levels of FAP in the tumor-associated stroma. The MoA of RO7300490 is also highly dependent on the number of available DCs co-located with FAP+ stroma. It has been demonstrated that a high degree of CD8+ T cell infiltration correlates positively with DC signatures ([Garris and Luke 2020](#)). [REDACTED] [REDACTED]

[REDACTED] In addition, the efficacy of RO7300490 will be

strongly dependent on intact presentation of antigens via major histocompatibility complex I (MHC I) molecules.

[REDACTED]

[REDACTED]

A combination of different methods such as, but not limited to, immunohistochemistry, immunofluorescence, and RNA sequencing will be employed to reach the objectives of biomarker detection and quantification in tumor tissue.

4.3 JUSTIFICATION FOR STARTING DOSE

The starting dose of RO7300490 will be 16 mg administered as IV infusion to participants with advanced and/or metastatic solid tumors following an initial Q2W administration schedule. This dose level was derived by integrating all information collected for RO7300490 from in vitro assessments, in vivo pharmacology and toxicology studies, in agreement with the European Medicines Agency guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products ([EMA Guideline 2018](#)). In addition, clinical safety and PK information available for other investigational CD40 agonist antibodies with similar MoA, with and without tumor targeting, such as selicrelumab (RO7009789, a non-targeted CD40 agonist Fc-gamma binding IgG2 antibody) and ABBV-428 (a mesothelin-targeted CD40 agonist IgG1 bispecific antibody) were considered. This starting dose is expected to be safe [REDACTED]

4.3.1 Supporting Non-clinical Safety Profile for RO7300490 and Comparison with Selicrelumab

Generally, given the lack of Fc- γ binding capacity and the unique ability to induce CD40 agonism only when cross-linked with FAP [REDACTED] ([RO7300490 Investigator's Brochure](#)), RO7300490 is expected to display a

favorable clinical safety profile, superior to what was observed for the non-tumor targeted CD40 agonist selicrelumab ([selicrelumab Investigator's Brochure](#)). This hypothesis is supported by favorable 4-week good laboratory practice (GLP) toxicology IV data obtained in cynomolgus monkeys [REDACTED]

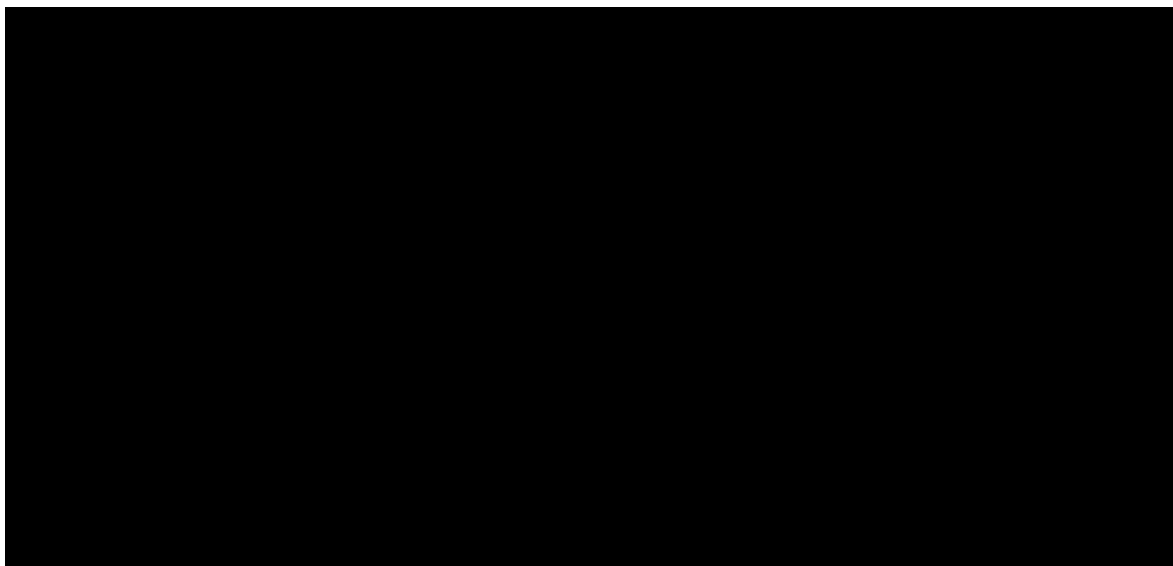
[REDACTED] In addition, it has been established that the CD40 distribution pattern in cynomolgus monkey and human blood is similar, further supporting the choice of cynomolgus monkeys as relevant species for human safety risk assessment of CD40 agonistic antibodies. FAP expression in cynomolgus monkeys and humans is also known to be comparable ([RO7300490 Investigator's Brochure](#)).

Similarly to the findings in cynomolgus monkeys, in vivo pharmacology experiments performed with [REDACTED] in [REDACTED] subcutaneous tumor bearing transgenic C57bl/6-huCD40 mouse model, demonstrated pharmacological activity in tumor that was not accompanied by either MoA-related toxicity in the liver or cytokines release in circulation up to the highest tested intraperitoneal dose [REDACTED] ([RO7300490 Investigator's Brochure](#)). The described systemic toxicities were observed for selicrelumab, which in the same mouse study at equimolar doses, induced body weight loss, increase in liver enzymes and hepatocellular injury, as well as a profound cytokine release in circulation ([RO7300490 Investigator's Brochure](#)).

4.3.2 Starting Dose Selection Based on in vivo MABEL

Rationale

Due to the immune agonist nature of RO7300490, the starting dose for RO7300490 was derived using the minimal anticipated biological effect level (MABEL) approach, based on the predicted minimal pharmacologically active dose (mPAD) in man, derived from in vivo pharmacology studies (“in vivo MABEL”). Of note, selection of starting doses based on in vivo mPAD (“in vivo” MABEL) has been used already for bispecific agonistic antibodies ([Driessen et al. 2019](#)).



Calculation Methods and Selected Starting Dose Value

The intravenous human mPAD for RO7300490 was estimated linking the predicted human clearance ranges with the minimal drug efficacious serum exposure derived from pharmacology studies in tumor-bearing mice ([RO7300490 Investigator's Brochure](#)). The predicted RO7300490 mPAD [REDACTED] for the Q2W administration schedule (lowest value from the projected minimally [REDACTED]) was then [REDACTED] to finally derive a starting dose of 16 mg IV, value, which does not exceed the MTD of selicrelumab in man ([selicrelumab Investigator's Brochure](#)).

Expected Human Exposure at Starting Dose and Margins vs. Toxicological Studies in Cynomolgus Monkeys

After the first IV infusion of RO7300490 at 16 mg, the serum C_{max} value in human for RO7300490 is expected to range [REDACTED] according to the assumptions for PK predictions ([RO7300490 Investigator's Brochure](#)). At these concentrations, the in vitro human whole blood assay did not identify a high risk of cytokine release for RO7300490. [REDACTED]

[REDACTED] Regarding the exposure margins, after IV administration of RO7300490 at 16 mg, the predicted Cycle 1 C_{max} and AUC in patients are both > 1000-fold below the C_{max} and AUC values observed at the [REDACTED] [REDACTED] in the cynomolgus monkey GLP toxicity study ([RO7300490 Investigator's Brochure](#)).

In summary, taking into account that RO7300490 showed a considerably more favorable non-clinical safety profile [REDACTED]

[REDACTED] it is expected that the in vivo MABEL-derived starting dose for RO7300490 of 16 mg (approximately 0.23 mg/kg for a patient of 70 kg) will be clinically safe.

4.3.3 Rationale for Initial Dose Administration Frequency

RO7300490 will be initially administered IV Q2W. This dosing regimen, which might be adjusted if deemed necessary according to emerging clinical data, has been suggested by PK/PD modeling activities simulating dynamic engagement of the pharmacologically active species, i.e., the ternary complex (TC), which is expected to be formed in tumor between FAP, RO7300490, and the CD40 receptor. These TC PK/PD simulations, addressing the first step toward the pharmacological effect of RO7300490 at tumor site, and their application to the development of bispecific antibodies is increasing.

Indeed, because of the complex MoA of bispecific antibodies, mathematical approaches describing the simultaneous drug-mediated engagement of two targets in tumor are considered scientifically more appropriate to inform on optimal bispecific antibodies dose and scheduling than the classical single receptor occupancy calculations ([Betts and van der Graaf 2020](#), [Schropp et al. 2019](#)). [REDACTED]

[REDACTED] The output reflects the potential time-dependent fluctuation of the percent (%) of TC engagement in the tumor and is available for a wide dose range after Q1W, Q2W, and Q3W regimens. Based on these initial assumptions, following a dosing regimen of Q2W IV, the TC engagement in tumor is expected to reach

its maximal level [REDACTED]

4.4 END OF STUDY DEFINITION

The end of this study is defined as the date when the last participant, last visit occurs or the date at which the last data point required for statistical analysis or protocol-defined safety follow-up for the last participant is received, whichever is the latest date. A participant is considered to have completed the study if he/she has completed all phases of the study, including the scheduled safety follow-up visit after the last dose of study treatment, also in case of premature treatment discontinuation.

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

5. STUDY POPULATION

The participants in this study will be adult patients diagnosed with locally [REDACTED]
[REDACTED] solid tumors [REDACTED]

The study population rationale is provided in Section [4.2.1](#).

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

5.1 INCLUSION CRITERIA

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

1. Signed informed consent form (ICF).
2. Age \geq 18 years.
3. Life expectancy of \geq 12 weeks.
4. Histologically confirmed diagnosis of locally advanced and/or metastatic solid tumors that are not amenable to standard therapy.

5. **For Part 1 and Part 2:** diagnosis of locally advanced and/or metastatic solid tumor types including NSCLC, SCLC, TNBC, cutaneous melanoma, *urothelial cancer (including renal pelvis, ureters, urinary bladder and urethra)*, mesothelioma, HCC, HNSCC, ESCC, and cervical SCC.
6. Radiologically measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1:
 - Participants must have at least one measurable target lesion (TL) not intended to be biopsied.
 - Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion and no other target lesions are available.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.
8. Ability to comply with the protocol requirements.
9. **For participants enrolled in Part 1 and Part 2 (only in cohorts with mandatory biopsies):** willingness to provide mandatory fresh screening and on-treatment biopsies as well as archival tumor samples acquired within ≤ 12 months (when available) from a safely accessible site, per Investigator determination and patient consent, provided the patient has more than one measurable target lesion. The biopsied lesion must not be a target lesion.
10. **For participants enrolled in Part 3:** [REDACTED]
11. Adequate cardiovascular function, including:
 - New York Heart Association (NYHA) Heart Failure Stage ≤ 2 .
 - Left ventricular ejection fraction $\geq 50\%$, as determined by multiple-gated acquisition scan, transthoracic echocardiogram, or cardiac MRI (cMRI). This applies to participants with cardiovascular conditions in their medical history and all participants aged > 50 years.
 - Baseline-corrected QT (QTcF) interval ≤ 470 ms.
 - Resting systolic blood pressure ≤ 150 mm Hg and diastolic blood pressure ≤ 100 mmHg (average of ≥ 3 readings on ≥ 2 sessions).
 - Resting heart rate (HR) between 45-100 bpm.
12. Adequate hematological function, including:
 - Neutrophil count of $\geq 1.5 \times 10^9$ cells/L.
 - Platelet count of $\geq 100 \times 10^9$ /L.
 - Hemoglobin ≥ 9 g/dL (5.6 mmol/L).
 - Lymphocyte count $\geq 0.5 \times 10^9$ cells/L.
13. Adequate liver function, including:

- Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN; $\leq 3 \times$ ULN in participants with Gilbert syndrome) or direct bilirubin \leq ULN for participants with total bilirubin levels $> 1.5 \times$ ULN.
- AST, ALT, alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN, with the following exceptions:
 - Participants with documented liver metastases: AST and ALT $\leq 5 \times$ ULN.
 - Participants with documented liver or bone metastasis: ALP $\leq 5 \times$ ULN.

14. Adequate renal function:

- Serum creatinine $\leq 1.5 \times$ 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.

Cockcroft-Gault formula: estimation of glomerular filtration rate

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

15. Adequate coagulation function and other laboratory values, defined as:

- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN or $\leq 2 \times$ ULN for participants with hepatocellular carcinoma.
- For participants receiving therapeutic anticoagulation: stable anticoagulant regimen.
- Serum albumin ≥ 25 g/L.

16. Adequate contraception

Male or female participants agree to use contraception or abstinence requirements 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.

Female Participants: A female participant is eligible to participate if she is not pregnant, not breastfeeding or lactating, and at least one of the following conditions applies:

- Women of non-childbearing potential (WONCBP), as defined in [Appendix 5](#).
or
- Women of childbearing potential (WOCBP), who:
 - Agree to remain abstinent (refrain from heterosexual intercourse) or
 - Use of two highly effective contraceptive methods (including bilateral tubal occlusion, male partner sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices [IUDs] and copper IUDs) that result in a failure rate of

<1% per year during the treatment period and for at least 2 months after the final dose of RO7300490, for at least 3 months after the final dose of tocilizumab (if applicable), and at least 5 months after the final dose of atezolizumab (if applicable), whichever is longer.

- Hormonal contraceptive methods must be supplemented by a barrier method.
- Refrain from donating oocytes during the study treatment and for the specified months after treatment discontinuation (as indicated above).
- Female participants should seek advice on conservation of oocytes prior to treatment initiation because of the potential effect of RO7300490 on fertility.
- Have a negative serum pregnancy test at screening (within 14 days of study treatment start).
- Have a negative urine pregnancy test prior to the first dosing.

Male Participants: During the treatment period and for at least 2 months after the final dose of RO7300490 or at least 2 months after the final dose tocilizumab (if applicable), whichever is longer, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or
- Use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of <1% per year, with partners who are WOCBP, as defined in [Appendix 5](#).
- Refrain from donating sperm during that period.
- Male participants should seek advice on conservation of sperm prior to treatment initiation because of the potential effect of treatment with RO7300490 on fertility.
- With pregnant female partners (if applicable), remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo. Hormonal contraceptive methods must be supplemented by a barrier method, as defined in [Appendix 5](#).

5.2 EXCLUSION CRITERIA

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

1. Known central nervous system (CNS) primary tumors or metastases, including leptomeningeal metastases, unless *the following conditions are met: they have been previously treated and are asymptomatic, are stable (without evidence of progression by computed tomography (CT) or magnetic resonance imaging (MRI) for at least 28 days prior to the first dose of the study drug)* and have had no requirement for systemic steroids or enzyme-inducing anticonvulsants in the last 14 days prior to screening.
2. Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 14 days before C1D1.

3. Active second *invasive* malignancy *within two years prior to screening* (exceptions are non-melanoma skin cancer, cervical carcinoma in situ, *ductal carcinoma in situ of the breast*, or prostate carcinoma that is in remission under androgen deprivation therapy for > 2 years)
4. All acute toxic effects of any prior radiotherapy, chemotherapy, targeted or checkpoint inhibitor therapy or surgical procedure must have resolved to Grade ≤ 1 or returned to baseline, except for alopecia (any grade), for Grade 2 clinically controlled sequelae of immune-related toxicities related to checkpoint-inhibitor therapy like adrenal insufficiency and hypopituitarism, and for Grade 2 peripheral neuropathy.
5. Significant cardiovascular/cerebrovascular disease within 6 months prior to C1D1 of study drug administration, including any of the following:
 - Hypertensive crisis/encephalopathy.
 - Unstable angina pectoris.
 - Transient ischemic attack/stroke.
 - Congestive heart failure III or IV (for NYHA classification, refer to inclusion criteria).
 - Serious cardiac arrhythmia requiring treatment (*with the exception of atrial fibrillation*).
 - History of thromboembolic events (such as myocardial infarction, stroke or *symptomatic and/or clinically significant pulmonary embolism*).
6. Known hereditary or acquired coagulopathies (e.g., hemophilia, von Willebrand disease, clinically manifested cancer-associated diffuse intravascular coagulation).
7. History of idiopathic pulmonary fibrosis, pneumonitis (including drug-induced), interstitial lung disease, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active interstitial lung disease/pneumonitis on screening chest CT scan.
History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
8. Severe dyspnea at rest or requiring supplementary oxygen therapy.
9. Known clinically significant liver disease including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease.
10. Active or history of autoimmune disease including, but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis, with the following exceptions:
 - Participants with a history of autoimmune-mediated hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
 - Participants *on replacement doses of corticosteroids to manage hypopituitary or adrenal insufficiency 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 less than 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 within the last 12 months (e.g., not requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids).
11. Known active or uncontrolled bacterial, viral, fungal, mycobacterial (including but not limited to tuberculosis and atypical mycobacterial disease), parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 28 days prior to the start of study drug administration.
 12. Known human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection at screening.
 - *HBV: Participants must present a negative hepatitis B surface antigen (HBsAg) test, and a negative total hepatitis B core antibody (HBcAb).* Participants with positive total HBcAb test followed by a negative HBV DNA test at screening can be enrolled.
 - *HCV: 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. History of severe allergic or anaphylactic reactions to mAb therapy (or recombinant antibody-related fusion proteins).
 14. Known hypersensitivity to any of the components of RO7300490 formulation or to components of atezolizumab formulation.
 15. Prior allogeneic bone marrow transplantation or prior solid organ transplantation.
 16. Pregnancy, lactation, or breastfeeding.
 17. Dementia or altered mental status that would prohibit informed consent.
 18. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug.
 19. Major surgery or significant traumatic injury within 28 days prior to the first study drug administration (excluding biopsies) or anticipation of the need for major surgery during study treatment.

20. Treatment with radiotherapy, chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or investigational drug (defined as a treatment for which there is currently no regulatory authority–approved indication) concurrent or within 28 days or 5 half-lives of the drug (whichever is shorter) before the first study drug administration (C1D1).
21. Previous treatment with any other compound that targets CD40 (e.g. selicrelumab [RO7009789], Chi Lob 7/4, mitazalimab [ADC-1013]).
22. Regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease) or treatment with systemic immunosuppressive medications (including, but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents) within 14 days prior to first study drug administration, with the following exceptions:
 - Participants who received acute and/or low-dose systemic immunosuppressive medications (e.g., a one-time dose of dexamethasone for nausea or *48 hours maximum of corticosteroids as premedication for a contrast allergy or short-term use of ≤ 10 mg/day of prednisone or dose-equivalent corticosteroid*) are eligible for the study.
 - The use of inhaled or topical corticosteroids is allowed.
23. Treatment with systemic immune-modulating agents, including but not limited to etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, or efalizumab within 28 days or 5 half-lives of the drug (whichever is shorter) before the first study drug administration (C1D1).
24. Radiotherapy within the last 28 days before the first study drug administration, with the exception of limited field palliative radiotherapy.
25. Administration of a live, attenuated vaccine within 28 days prior to the first study drug administration.

5.3 LIFESTYLE CONSIDERATIONS

Participants are expected to adhere to the protocol requirements regarding contraception, but there are no other lifestyle restrictions during the study. There are no study-specific restrictions to meals and dietary practices.

5.4 SCREEN FAILURES

Screen failures are defined as patients, who consent to participate in the study, but are not subsequently enrolled in the study. Screen failures may be tracked separately.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Individuals who passed the screening but could not be enrolled within the 28-day screening window due to a study halt, logistical, personal, or technical reasons may be re-screened. In the event re-screening is permitted, invasive assessments like biopsies do not have to be repeated, following documented consultation with the Medical Monitor.

In case of uncertain or questionable results, any of the tests performed during screening may be repeated before study treatment administration to confirm eligibility or clinical significance. In the event that a participant is not enrolled into the study, any tumor sample that was sent to the Sponsor will be returned to the site (preferably, all screening assessments should be confirmed before a biopsy is collected).

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment by the local investigators using pre-screening enrollment logs, clinical databases and Independent Ethics Committee (IEC)/Independent Review Committee (IRB) approved newspaper/radio/social-media advertisements. An Interactive Response Technology (IRT) system will be utilized to manage pre-screening (e.g. cohort management), screening and enrollment. This process controls the entry of participants into each cohort.

After the participant signed the informed consent, all screening assessments must be completed and reviewed at the site to confirm that participants meet all eligibility criteria. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site. The screening transaction should be performed in the IRT system (including reasons for screening failure if applicable), an Eligibility Screening Form documenting the Investigator's assessment of each screened participant with regard to the protocol inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site. Upon confirmation of eligibility, the participants will be enrolled using the IRT system.

The login information and instructions for use of the IRT will be provided to each site.

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.

The investigational medicinal products (IMPs) for this study are RO7300490, atezolizumab, and tocilizumab (Actemra®, RoActemra®).

Tocilizumab is considered as a rescue medication only, which may be used (if needed) after the administration of RO7300490 for the treatment of severe or life-threatening CRS. Use of commercial tocilizumab may be permitted under certain circumstances (e.g., for emergency use) and if approved by the national and/or local Health Authorities as applicable.

All IMPs required for completion of this study will be provided by the Sponsor. Every study drug administration will be performed at the study site under the supervision of trained site staff. Cases of accidental overdose or medication error, along with any associated AEs, must be reported as described in [Appendix 2](#).

Pre-medications and rescue medications (with the exception of tocilizumab) are non-IMPs (NIMPs) in this study.


6.1 TREATMENTS ADMINISTERED

Because infusion of therapeutic antibodies may cause IRRs (as a defined in Section 8.3.9), study treatments must be administered in a clinic or hospital equipped for systemic cancer treatment. There must be immediate access to trained medical staff and adequate equipment and medicine to manage potentially serious reactions. Full emergency resuscitation facilities must be immediately available and participants must be under close observation by the Investigator at all times. In case of occurrence of IRRs/CRS, the symptoms should have fully resolved before the participant is discharged.

The IMPs and their characteristics are summarized in Table 9. For more details on RO7300490 and atezolizumab, refer to the respective Investigator's Brochures and the Pharmacy Manual. For more information on tocilizumab, refer to the tocilizumab Investigator's Brochure.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively. RO7300490 and atezolizumab dosing will only occur if a participant's clinical assessment and laboratory test values are acceptable.

Table 9 Summary of IMPs

Study Drug Name:	RO7300490	Atezolizumab	Tocilizumab
IMP and NIMP	IMP	IMP	IMP
Dose Formulation:	Solution	Solution	Solution
Unit Dose Strength (Vial Strength):		60 mg/mL (1200 mg/vial)	20 mg/ml (200 mg/vial)
Dose:	Ascending doses Lowest dose: 16 mg	840 mg (Q2W) 1200 mg (Q3W)	8 mg/kg IV \geq 30 kg 12 mg/kg IV $<$ 30 kg Maximum dose 800 mg (irrespective of body weight)
Route of Administration:	IV	IV	IV
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor, except under extenuating circumstances (see Section 6)

6.1.1 RO7300490 Administration

RO7300490 will be administered by IV infusion as a single agent (Part 1) or in combination with atezolizumab (Parts 2 and 3). The dose of RO7300490 for each participant will depend on a dose level assignment, as detailed in Section 4.1.2.

The first dose of RO7300490 (C1D1) will be delivered over 120 ± 15 minutes. The IV line should remain in place for 90 minutes after the end of the infusion. Participants must stay in the clinic under close monitoring for at least 8 hours from the start of the infusion. During this time, participants will undergo close monitoring. Those participants who experience Grade ≥ 1 IRRs or Grade ≥ 1 tumor inflammatory events should stay in the hospital for at least 24 hours. If Grade ≥ 1 IRRs or Grade ≥ 1 tumor inflammatory events occur in a substantial number of participants during dose-escalation, mandatory hospitalization may be considered for newly enrolled participants as agreed between Sponsor and Investigator(s).

If the 120-minute infusion is tolerated without Grade ≥ 2 IRR/CRS, the second infusion (C2D1) *will* be delivered over 90 ± 15 minutes, followed by a 60-minute observation period. If the 90-minute infusion is well-tolerated (no Grade ≥ 2 IRR/CRS), all subsequent infusions *will* be delivered over 30 ± 10 minutes, followed by a 30-minute observation period. From C2 onwards and if no AE occurred in the previous cycle(s), the IV line should remain in place for at least 30 minutes after the end of each infusion (Table 10).

In the event of intra-participant dose escalation, including intra-participant dose escalation at the time of transfer from the imaging sub-study to the main study, infusion and observation times of the first and second infusions at the higher dose should be administered as if the participant were undergoing Cycle 1 and Cycle 2 infusions, respectively, per Table 10. From the third infusion at the higher dose onwards, and if the previous 2 infusions were well-tolerated (no Grade ≥ 2 IRR/CRS), study drug delivery will continue per Cycle 3 guidance in Table 10. Section 4.1 describes conditions required for intra-participant dose escalation.

Table 10 RO7300490 Infusion and Observation Times

RO7300490	Infusion Time	Post-infusion Observation
Cycle 1	120 (± 15) minutes	Total monitoring time post-infusion: minimum 6 hours, with IV line in place for ≥ 90 minutes after the end of the infusion.
Cycle 2, if no Grade ≥ 2 IRR/CRS in previous cycle	90 (± 15) minutes	≥ 60 minutes
Cycle 3 onwards, if no Grade ≥ 2 IRR/CRS in previous cycles	30 (± 10) minutes	≥ 30 minutes

CRS = cytokine release syndrome; IRR = Infusion-related reaction; IV = intravenous.

Vital signs (HR, respiratory rate, blood pressure, and temperature) must be monitored before, during, and after RO7300490 infusion, as described in Section 8.2.2 and the SoAs (Section 1.3).

For pre-medication required prior to RO7300490 dosing, refer to Section 0.

In case of adverse reactions during or after RO7300490 administration, including IRR/CRS, symptoms are to be treated according to medical judgment and institutional guidelines, considering the AE management guidelines in Section 8.3.9.

For a comprehensive list of potential risks associated with the study drug as single agent or in combination with atezolizumab, refer to the [RO7300490 Investigator's Brochure](#). For detailed instructions on RO7300490 preparation, storage, and administration, refer to the Pharmacy Manual.

RO7300490 Administration in Combination with Atezolizumab (Part 2 and 3 only)

Atezolizumab and RO7300490 will be administered on the same day. RO7300490 must be administered after atezolizumab. In addition, an observation period of at least 120 minutes after the end of the first atezolizumab infusion (C1D1), and at least 60 minutes after the end of the subsequent atezolizumab infusions (C2D1 onwards), is required before starting RO7300490 infusion. Participants must have recovered from any acute toxicity mediated by the preceding administration of atezolizumab before receiving RO7300490.

In the initial cycles of combination treatment with long infusion and observation times and/or in the event that RO7300490 infusion following atezolizumab must be delayed, an overnight hospitalization may be considered.

6.1.2 Atezolizumab Administration

Atezolizumab will be administered only in Parts 2 and 3 (prior to RO7300490 administration, [Table 11](#)). Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on day 1 of each Q2W cycle (or 1200 mg on Day 1 of each Q3W cycle).

The first dose of atezolizumab (C1D1) will be delivered over 60 ± 15 minutes. If the first infusion is tolerated without Grade ≥ 2 IRR, the second infusion (C2D1) may be delivered over 30 ± 10 minutes. In case the 30-minute infusion is well-tolerated, all subsequent infusions (C3 onwards) may be delivered over 30 ± 10 minutes.

Participants should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Table 11 Atezolizumab Infusion and Observation Times

Atezolizumab	Infusion Time	Post-infusion Observation
Cycle 1	60 (± 15) minutes	≥ 120 minutes
Cycle 2 onwards, if no Grade ≥ 2 IRR in previous cycle(s)	30 (± 10) minutes	≥ 60 minutes

Vital signs (HR, respiratory rate, blood pressure, and temperature) must be monitored as described in section 8.2.2 and the SoA (Section 1.3).

For pre-medication required prior to atezolizumab administration, see Section [6.1.5](#).

Guidelines for treatment interruption or discontinuation for participants who experience atezolizumab-associated AEs and guidelines for medical management of atezolizumab-associated AEs, including IRRs, are provided in the [Appendix 10](#).

No dose modification for atezolizumab is allowed.

For detailed instructions on drug preparation, storage, and administration, refer to *the* current version of the [atezolizumab Investigator's Brochure](#) and the Pharmacy Manual.

6.1.3 Tocilizumab Administration

Tocilizumab (RO4877533, Actemra/RoActemra) is a recombinant, humanized, anti-human mAb directed against soluble and membrane-bound IL-6R, which inhibits IL-6 mediated signaling ([Singh et al. 2011](#)). Blocking the inflammatory action of IL-6 using tocilizumab is approved for the treatment of CAR-T cell-induced severe or life-threatening CRS ([Tocilizumab Investigator's Brochure](#)).

There have been multiple reports in the literature of tocilizumab being used off-label to successfully treat severe or life-threatening CRS ([Teachey et al. 2013](#); [Lee et al. 2014](#); [Le et al. 2015](#)), and it is becoming a recommended rescue for the treatment of CRS after CIT medication within clinical studies. CRS is a potential risk for RO7300490; therefore, tocilizumab will be administered if required, for the management of severe or life-threatening CRS.

Tocilizumab will be administered at 8 mg/kg IV single dose (for participants with a body weight ≥ 30 kg), or 12 mg/kg IV single dose (for participants with a body weight < 30 kg). The maximal total dose for tocilizumab should not exceed 800 mg, irrespective of the body weight. Rescue treatment may be repeated every 8 hours as necessary (up to a maximum of four doses). These dose recommendations are based on previous clinical experience with tocilizumab in the context of severe CRS mitigation and are further described in the [tocilizumab Investigator's Brochure](#).

The SoA for tocilizumab treatment is in [Appendix 11](#).

For details on drug preparation, storage, and administration, refer to the [tocilizumab Investigator's Brochure](#) and the Pharmacy Manual. In an emergency situation in which commercial tocilizumab is used, refer to the local prescribing information.

6.1.4 Pre-medication for Participants Receiving RO7300490

Pre-medication is not foreseen before the first administration of RO7300490. Based on emerging data during dose-escalation (e.g. if Grade ≥ 2 IRR/CRS occur in the majority of participants) the use of prophylactic pre-medication may be implemented, if the

Investigator(s) and the Sponsor agree that pre-medication is expected to mitigate the observed toxicities.

Participants who experienced a Grade 2 or higher IRR/CRS on a previous infusion should be pre-medicated for subsequent infusions with an antihistamine (H1-receptor antagonist), anti-pyretics (acetaminophen 500 mg to 1000 mg orally/IV or alternatively ibuprofen 400-600 mg orally or other nonsteroidal anti-inflammatory drugs per institutional standard if acetaminophen cannot be tolerated), an anti-emetic, and hydration with 500 mL crystalloid fluid. If a participant experiences a Grade 3 IRR, the same will apply and 200 mg hydrocortisone IV (or equivalent dose of another corticosteroid) are added. Pre-medication regimens for subsequent cycles may be reduced or omitted in case of Grade ≤ 1 events in the previous cycle.

If a participant experiences an isolated episode of fever during or within 24 hours after RO7300490 administration, and if it is judged to be related to study drug infusion, it should be reported as CRS per [Appendix 3](#) and [Appendix 9](#). The treatment and management (guidance in [Section 8.3.9.1](#) and [Table 13](#)) at the time of such a single and isolated event is at the discretion of the Investigator. Pre-medication for those participants at subsequent infusions should be considered.

The use of prophylactic pre-medication should be discussed with the Medical Monitor and decision documented, and all pre-medications have to be captured as concomitant medications in the participant's pre-medication eCRF.

6.1.5 Pre-medication for Participants Receiving Atezolizumab

No pre-medication is indicated before the first administration (C1D1) of atezolizumab.

Participants who experience an IRR with any previous infusion of atezolizumab may receive pre-medication with antihistamines, antipyretics and/or analgesics at the discretion of the Investigator. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRR, because of its potential for causing agranulocytosis. For more details, refer to [Appendix 10](#).

All pre-medications have to be captured in the participant's pre-medication eCRF.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The packaging and labeling of the study medication will be done in accordance with the Sponsor's standard and local regulations. Study drug packaging will be overseen by the Sponsor's clinical study supplies department and labelled with the identification required by local law, including (but not limited to) the protocol number, drug identification, dosage, and expiration date.

The study site must follow all instructions included with each shipment of IMP. The Investigator or other authorized personnel (e.g., pharmacist) will acknowledge receipt of

IMPs and confirm shipment condition and content. Any damaged shipment will be replaced. The Investigator or its designee must confirm that appropriate temperature conditions have been maintained during transport for all IMPs received and that any findings, product complaints, or discrepancies were reported to the Sponsor and resolved before use of the IMP. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions and where access is limited to the Investigator and authorized staff.

Only participants enrolled in the study may receive IMPs and only authorized site staff may supply or administer IMPs. The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the Pharmacy Manual, based on the treatment, dose and schedule, individually assigned to each participant.

The Investigator is responsible for IMP accountability (i.e., receipt, reconciliation, and final disposition records). The study site (i.e., Investigator or other authorized personnel [e.g., pharmacist]) will maintain accurate records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP. This will enable reconciliation of all IMPs received and ensure that participants are provided with the doses, which are specified in the protocol and the IRT system.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure upon written approval by the Sponsor, or returned to the Sponsor with the appropriate documentation. 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 will be recorded on the drug accountability log.

For information on RO7300490 IMP formulation, IMP handling, including preparation, storage, and accountability, refer to the Pharmacy Manual and/or the [RO7300490 Investigator's Brochure](#). For information on [atezolizumab](#) or [tocilizumab](#) IMP formulation, handling (including preparation and storage), and accountability, refer to the Pharmacy Manual and respective Investigator's Brochures.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

Study WP42627 is an open-label study; however, the specific treatment administered to a participant will be assigned using IRT to reduce potential bias in the assignment to a specific study cohort and/or part.

The site will contact the IRT system prior to the start of study treatment administration for each participant. If open slots are available in more than one cohort and/or part at the

same time and if, according to the inclusion/exclusion criteria, the prospective participant could be enrolled in more than one of the enrolling cohorts and/or parts, the participant will be randomized to a cohort and/or part using the IRT system.

6.3.2 Blinding

This is an open-label study. Blinding procedures are not applicable.

6.4 TREATMENT COMPLIANCE

The qualified staff member responsible for dispensing the study treatment will prepare the correct dose according to the Pharmacy Manual, based on the treatment assigned to each participant. This staff member will keep a record of the participant number, the assigned study treatment, date dispensed and any other relevant information for each dispensed IMP.

6.5 CONCOMITANT THERAPY

Any medication or non-live vaccine (including over-the-counter or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant within 28 days prior to study screening until the safety 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). The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All concomitant medications will be reported to the Investigator and recorded on the Concomitant Medications eCRF. All medications administered to manage AEs will be recorded on the AE eCRF. If tocilizumab is administered to manage CRS, its use will be recorded in the tocilizumab eCRF.

6.5.1 Permitted Therapy

Participants who use oral contraceptives with a failure rate of < 1% per year (see [Appendix 5](#)), hormone-replacement therapy, or other maintenance therapy should continue their use.

Systemic corticosteroids and immune suppressants may attenuate potential beneficial immunologic effects of treatment with RO7300490 and atezolizumab but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered.

Topical corticosteroids as well as eye drops and inhalers containing corticosteroids may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered.

The use of limited field palliative radiotherapy is allowed at any time during the study, except on days when RO7300490 is administered and during DLT-evaluation period. If radiotherapy is administered during the DLT evaluation period, the participant will not be

evaluable; however, study treatment may be continued should the Investigator after documented consultation with the Medical Monitor, evaluates that the participant may benefit from further dosing.

Inactivated vaccines (i.e., non-live vaccines, *including those for influenza and COVID-19*) are allowed during the course of the study. The efficacy and safety of non-live vaccines in participants receiving treatment with RO7300490 is unknown. Ultimately, for each participant, the decision to receive a non-live vaccine will be a benefit risk discussion between the participant and treating physician. This decision will depend on a number of factors, such as the type of non-live vaccine, the potential risk of infection, and the underlying disease and age of the participant. The timing of administration of a non-live vaccine during the course of the study can be discussed with the Medical Monitor if warranted and should be documented, if it occurs.

There is no data on potential interactions of non-live vaccines with RO7300490. In the absence of evidence-based recommendations, it would be advisable to space enough time between the administration of the non-live vaccine and RO7300490 in order to minimize the potential confounding effect of the non-live vaccine. In particular, administration of non-live vaccines should be avoided on the day of RO7300490 administration and on days close to RO7300490 administration. In addition, administration of non-live vaccines should be avoided during the DLT observation window or during the first cycle for fixed dose regimens. AEs that may overlap with any potential vaccine-related toxicities should have resolved before patients receive non-live vaccines.

6.5.2 Prohibited Therapy

In general, no concomitant medication will be permitted, with the exception of medications to treat AEs and therapy for pre-existing conditions, unless the rationale for exception is discussed and clearly documented between Investigator and the Sponsor.

For a list of prohibited therapies within 28 days prior to RO7300490 and/or atezolizumab administration, refer to the exclusion criteria (Section [5.2](#)).

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, targeted therapy, hormonal therapy, immunotherapy, radiotherapy, radio- immunotherapy.
- Radiotherapy may be considered for pain palliation as described in Section [6.5.1](#).

The following therapies are prohibited while participants are receiving RO7300490 and/or atezolizumab:

- Immunostimulatory agents (including, but not limited to, interferons or IL-2).
- Immunosuppressive medications including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide.
- Chronic use of steroids (excluding topical and inhaled) and concurrent high doses of systemic corticosteroids with the exception of their use to treat AEs (as per institutional guidelines). Acute and/or low-dose systemic immunosuppressive medications (e.g. a one-time dose of dexamethasone for nausea or *48 hours maximum of corticosteroids as premedication for a contrast allergy or short-term use of ≤ 10 mg/day of prednisone or another dose-equivalent corticosteroid*) are allowed.
- Administration of a live, attenuated vaccine.
- Metamizole (dipyrone) is prohibited to treat atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

6.6 DOSE AND SCHEDULE MODIFICATION

In general, there will be no dose modifications for RO7300490 and/or atezolizumab in this study. Administration of RO7300490 or RO7300490/atezolizumab combination may be temporarily suspended in participants who experience toxicity during study treatment. In the event a dose reduction is necessary for treatment-emergent AEs, documented consultation with the Medical Monitor and the Investigator of all decisions regarding dosing and dose-schedule modifications is required. Management guidelines, including study treatment dose and schedule modifications for specific AEs, are described in Section 8.3.9 and [Appendix 10](#).

The following guidelines regarding dosing and dose-schedule modifications should be followed:

- Participants who experience a DLT should discontinue the study treatment. Nevertheless, the Investigators, after documented consultation with the Sponsor, will have the option to continue treatment with a reduced dose of RO7300490 in selected participants after recovery from the DLT. This can be done to allow participants who could potentially benefit from RO7300490, as a single-agent or in combination, to remain on the study treatment.
- For participants who experience AEs that require RO7300490 and/or atezolizumab dose schedule to be interrupted, D1 of the next cycle may be delayed for up to 2 cycles (i.e., 28 days with a Q2W schedule, or 42 days with a Q3W schedule), in order to recover from toxicity. If, in the judgment of the Investigator, the participant is likely to derive clinical benefit from RO7300490 as single agent or in combination with atezolizumab after a hold of > 2 cycles, study treatment may be restarted after documented consultation with the Medical Monitor; otherwise, the participant should permanently discontinue all study treatment.
- In general, participants receiving RO7300490 and/or atezolizumab who experience a Grade 4 AE that is not considered by the Investigator to be attributable to another

clearly identifiable cause should permanently discontinue all study treatment. However, for participants with Grade 4 AEs of asymptomatic laboratory changes, study treatment may be resumed upon resolution to Grade ≤ 1 or baseline after documented consultation with the Medical Monitor.

- If a participant must be tapered off steroids used to treat AEs, atezolizumab and RO7300490 may be withheld for additional time beyond 2 cycles until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The Investigator will decide on acceptable length of interruption upon documented consultation with the Medical Monitor.

Any dose-schedule modification should be noted on the Study Drug Administration eCRF.

6.7 TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide RO7300490 or any other study treatment or interventions to participants after the end of the study or any earlier participant withdrawal. The Sponsor will evaluate the appropriateness of continuing to provide study treatment to participants after the conclusion of the study, in accordance with the Roche Global Policy on Continued Access to IMP and in accordance with local regulations. This Roche Global Policy is 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, including the safety follow-up assessment, as outlined in this protocol.

Detailed procedures for study discontinuation (as a whole) and site closures are provided in [Appendix 1](#).

7.1 DISCONTINUATION OF STUDY TREATMENT

Participants will be treated for 24 months (the treatment period may be modified by the Sponsor if supported by emerging data) or until they experience any of the following:

- Toxicities fulfilling the criteria of a DLT as per Section [4.1.3](#).
- Disease progression as defined per RECIST 1.1.
- Any toxicity, which is not manageable with dose schedule delays (as allowed per protocol), and/or appropriate treatment.

- Grade 4 IRR/CRS for RO7300490 and/or atezolizumab (except for circumstances detailed in [Table 13](#) and in [Table 7](#) of Appendix 10).
- IgE-mediated hypersensitivity reactions, including anaphylaxis.
- Any medical condition that the Investigator or Sponsor determines that it may jeopardize the participant's safety if he or she continues to receive study treatment.
- Loss of clinical benefit.
- Pregnancy.

Participants who discontinue study treatment (either prematurely or after study treatment completion as per protocol) will be asked to return to the site for an end of treatment (EoT) visit and will undergo follow-up assessments as defined in the SoA (Section [1.3](#)) and Section [8.11.5](#), unless the participant withdrew his/her consent to the study.

The primary reason for study treatment discontinuation has to be documented on the appropriate eCRF. Every effort should be made to obtain information on participants who refused further study treatment but have not withdrawn consent.

As with other immunotherapies, treatment beyond initial image evidence of disease progression as per RECIST v1.1 ([Appendix 8](#)) should be considered until confirmed progression on the subsequent tumor assessment. Treatment beyond confirmed disease progression as per immune RECIST (iRECIST) v1.1 ([Appendix 7](#)) could be considered following documented consultation between the Sponsor and Investigator. The following criteria will have to be met for a participant to continue treatment beyond initial apparent progressive disease per RECIST v1.1 (e.g., radiological progression secondary to tumor inflammation):

- Absence of clinical deterioration.
- Investigator-assessed potential clinical benefit for the participant.
- The participant is tolerating study treatment.
- When considering treatment beyond progression, locally approved and available treatment options need to be taken into account.

7.1.1 Temporary Interruption

Temporary study drug interruption is an acceptable method to manage AEs related to any of the study treatments. These interruptions should be handled as described in Section [6.6](#).

Study treatment interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed after documented consultation with the Medical Monitor. The Investigator will decide on acceptable length of interruption upon documented consultation with the Medical Monitor.

If a scheduled dosing coincides with a holiday that precludes dosing, or if exceptional circumstances prevent the participant from attending, dosing should commence on the nearest suitable following date, with subsequent dosing continuing on a Q2W schedule (or Q3W as applicable). From Cycles 2 to 4, a treatment delay of 1 day at the start of a new cycle (i.e., Day 1) because of holidays, inclement weather, or other justifiable events, will be permitted and not considered as a protocol violation. From Cycle 5 onwards, a treatment delay up to 3 days at the start of a new cycle (i.e., Day 1) for the same reasons will be permitted and not considered as a protocol violation.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to withdraw voluntarily from the study at any time for any reason. In addition, the Investigator has the right to discontinue/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 discontinuation/withdrawal from the study should be obtained and documented on the appropriate eCRF. Participants will not be followed up for any reason after consent has been withdrawn.

When a participant voluntarily withdraws his/her consent to the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests these samples 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; see [Appendix 1](#)).

Participants who discontinue study treatment or withdraw from the study for safety reasons will not be replaced. Participants who prematurely discontinue study treatment or withdraw from the study for the following reasons may be replaced to ensure adequate numbers of evaluable participants:

- Participants who withdraw from the study prior to treatment start may be replaced and their data will not be entered into the database.
- Participants who are not evaluable for DLT during dose-escalation in Parts 1 and 2 (Section [4.1.3.1](#)).

In case of a major protocol violation, participants will be included in the safety population and contribute to the MTD and/or RDE determination, and they 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. In the event that treatment continuation is considered, the Investigator needs to consult the Medical Monitor.

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 study site must attempt to contact the participant and reschedule the missed visit as soon as possible.
- 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 have to 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.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time points are summarized in the SoAs (Section 1.3).

Participants who were transferred from the imaging sub-study to the WP42627 main study should follow the relevant SoAs for Part 1 or 2 (excluding the PD assessments: blood receptor occupancy and T/B/NK cells, plasma PD cytokines, tumor tissue), starting from C2D1. Of note, in case of unscheduled safety events (e.g., the participant experiences a Grade ≥ 3 IRR/CRS, Grade ≥ 3 hypersensitivity reaction, or a RO7300490-related Grade ≥ 2 AE leading to delay and/or discontinuation of RO7300490 administration), a safety plasma cytokine sample is to be collected for these transferred participants.

Protocol waivers or exemptions are not allowed.

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

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Tumor response will be evaluated according to RECIST v1.1 ([Appendix 8](#)) and may be evaluated according to iRECIST ([Appendix 7](#)), at the time-points indicated in the corresponding SoAs (Section 1.3).

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the Investigator based on the physical examinations and CT (or MRI) scans of chest, abdomen, and pelvis with IV

contrast unless contraindicated and oral contrast as appropriate per institutional standards at the time points defined in the SoAs (Section 1.3). Participants who have a contraindication to IV contrast may have MRI scans of the abdomen and pelvis performed in lieu of CTs and a non-contrast CT of the chest. If a CT scan for tumor assessment is performed in a PET-CT scanner, the CT acquisition must be of full diagnostic quality and include CT contrast. Ultrasound and X-rays are not acceptable for monitoring target lesions.

A CT or MRI scan (with IV contrast unless contraindicated) of the head must be performed at baseline to assess CNS metastases. 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 the participant has no brain metastasis at baseline, then *on-treatment* CT/MRI scan of the head is only indicated if symptoms suggest potential brain disease.

Tumor measurements should be made by the same Investigator/Radiologist for each participant to the extent that this is feasible and using the same assessment technique or procedure throughout the study (e.g., the same contrast protocol for CT scans). At the Investigator's discretion, CT (or MRI) scans may be repeated at any time if progressive disease is suspected (unscheduled tumor assessment).

In case of clinically superficial (such as skin) lesions, repeated photographs should be used to document tumor response. These photographs must include a ruler for documentation purposes (Section 8.1.2).

The data collected for RECIST v1.1 may be used by the Sponsor to derive time point responses for iRECIST (Appendix 7), 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 CIT field (Seymour et al. 2017). The derivation of iRECIST progressive disease status will be done manually and retrospectively.

Because of possible delayed onset of tumor response associated with immunotherapy treatment, as well as borderline progression, apparent radiologic progression with improving clinical status or mixed responses, 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 progression as per RECIST 1.1 could be considered until confirmed progression on the subsequent tumor assessment after documented consultation with the Medical Monitor.

Pre-study CT/MRI Scan

In addition to the screening scan, the latest pre-study or historical CT/MRI scan may be provided for assessment of tumor growth kinetics. The pre-study scan should not be older than 12 weeks prior to C1D1 (window: week -12 to day -29). This is an optional assessment.

An assessment of tumor growth kinetics will be made by comparing post-treatment scans with the latest pre-study or historical CT/MRI scan, if available, and the scan at screening.

8.1.2 Photography of Cutaneous Lesions

Cutaneous lesions not evaluable by CT or MRI will be documented by color digital photography, including a ruler to estimate lesion size. Cutaneous lesions may be considered target lesions if they meet RECIST 1.1 ([Appendix 8](#)); otherwise, they may be considered non-target lesions.

Photographs of cutaneous lesions will be taken at screening and the first clinic visit following each tumor assessment.

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoAs (Section [1.3](#)). On dosing days, the safety assessments are to be performed prior to the study treatment administration.

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest (NSAESI), measurement of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, electrocardiograms (ECGs), and other protocol-specified tests that are deemed critical to the safety evaluation of the study, as described in the subsections below. Assessments, which are not protocol-specified and are conducted by the Investigator in response to an AE (e.g. laboratory tests, etc.) can occur at any time during the study and may be shared with the Sponsor.

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

8.2.1 Physical Examinations

A physical examination will be performed at the visits indicated in the SoA and will include, at a minimum, an evaluation of the head, eyes, ears, nose, and throat including lymph nodes, and the cardiovascular, respiratory, gastrointestinal, genitourinary, dermatological, musculoskeletal, and neurological systems. At the Investigator's discretion, examination of other body systems may be performed in case of evocative

symptoms. The physical examination also includes body weight measurement. Height is to be collected at screening only.

As clinically indicated, a limited, symptom-directed physical examination should be performed during scheduled or non-scheduled visits between treatment days.

Any abnormality identified at baseline should be recorded in the participant's notes and captured on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities must be recorded as AEs on the AE eCRF.

8.2.2 Vital Signs

Temperature, heart rate, respiratory rate, and blood pressure will be assessed as outlined in the SoAs. Blood pressure and pulse measurements will be assessed in supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. When possible, the same arm should be used for all blood pressure measurements. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs should be taken after ECG measurement when scheduled at the same time point, *if possible*. At the discretion of the Investigator, vital signs can be repeated if the values are abnormal or borderline.

On the day of study treatment administration, vital signs should be monitored as follows:

RO7300490

- First and second infusion: Vital signs should be measured within 60 minutes prior to the infusion, every 15 (\pm 5) minutes during the infusion and 30 (\pm 10) minutes after the infusion.
- Subsequent infusions: Vital signs should be measured within 60 minutes prior to the infusion. If the participant experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and 30 (\pm 10) minutes after the infusion.

Atezolizumab

- First infusion: Vital signs should be measured within 60 minutes prior to the infusion. If clinically indicated, vital signs should be measured every 15 (\pm 5) minutes during the infusion and 30 (\pm 10) minutes after the infusion.
- Subsequent infusions: Vital signs should be measured within 60 minutes prior to the infusion. If the participant experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and 30 (\pm 10) minutes after the infusion.

Vital signs measured before and after treatment administration will be captured in the eCRFs. Vital signs measured during infusion will only be reported as AEs if they are abnormal. Not every vital sign abnormality qualifies as an AE. Criteria for vital sign results that should be reported as an AE are listed in Section 5 of [Appendix 3](#).

8.2.3 Eastern Cooperative Oncology Group Performance Status

It is recommended, where possible, that a participant's ECOG performance status be assessed by the same person throughout the study ([Table 12](#)).

Table 12 Eastern Cooperative Oncology Group Performance Status

Grade	ECOG
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 works 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

8.2.4 Electrocardiograms

Triplicate 12-lead ECG recordings (i.e., three qualitatively acceptable ECGs without artifacts within 10 minutes) will be obtained using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS complex, QT interval, and QT corrected for HR (QTc) intervals.

On the day of study treatment administration, measurements are to be done twice:

- Within 6 hours pre-infusion.
- Up to 30 minutes after the end of the infusion.

For participants receiving the combination treatment, pre-infusion measurements should be done before atezolizumab, whereas post-infusion measurements will be done after RO7300490 infusion. As clinically indicated, additional measurements may be done at the discretion of the Investigator.

To minimize variability, it is important that participants be in a resting and supine position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs will be performed prior dosing and should precede any scheduled vital sign measurements or blood draws.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement potentially contributing to the ECG abnormality. Additional unscheduled ECG assessments should be performed in case abnormalities and if clinical symptoms occur.

For safety monitoring purposes, the Investigator 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, as well as QTcF (Fridericia's correction), RR, and changes in T-wave and U-wave morphology, and overall ECG interpretation will be recorded on the eCRF. T-wave information will be captured as normal or abnormal and U-wave information will be captured as absent/normal or abnormal.

8.2.5 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in [Appendix 4](#) and these assessments must be conducted in accordance with the site's local laboratory requirements (where applicable) and the SoAs (Section 1.3). The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports will be filed as part of the participant's permanent study file at the site. Clinically significant abnormal laboratory findings are those, which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification), the results must be recorded in the CRF.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

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

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

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

8.2.6 Medical History and Demographic Data

Medical History includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, allergies and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 28 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

During the survival follow-up, any new anti-cancer treatments will be recorded.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity and causality) 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 as AEs but will be reported as baseline symptoms (General Medical History and Baseline Conditions eCRF).

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the safety follow-up visit, participant consent withdrawal, or initiation of other anti-cancer treatment or death, whichever occurs first. DLTs will be reported during the DLT assessment window (Section [4.1.3.1](#)).

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period.

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to the study treatment, at any time after the participant terminated 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 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 study-related procedures until a final outcome can be reported.

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

All pregnancies reported during the study should be followed up until pregnancy outcome and reported according to the instructions provided in Section [8.3.5](#).

8.3.3.2 Sponsor Follow-Up

For SAEs, NSAESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional event details and outcome information (e.g., from hospital discharge summaries, consultant reports,

autopsy reports) in order to perform an independent medical assessment of the reported event.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of 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, IRB/IEC, and Investigators.

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

An Investigator who receives an Investigator safety report describing 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 Investigator's Brochure 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 participants, access to the Medical Monitors is available 24 hours a day, 7 days a week. Details will be available separately.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to inform the Investigator immediately if they become pregnant during the study or within:

- 2 months after the last dose of RO7300490.
- 5 months after the last dose of atezolizumab (if applicable).
- 3 months after the last dose of tocilizumab (if applicable), whichever is longer.

Male participants will be instructed through the ICF to inform the Investigator immediately if their partner becomes pregnant during the study or within:

- 2 months after the last dose of RO7300490.
- 2 months after the last dose of tocilizumab (if applicable), whichever is longer.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and 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

NSAESI must 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).

NSAESI for this study include the following:

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

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

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

During the DLT-assessment window, AEs identified as DLTs (defined in Section [4.1.3](#)) must be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; for reporting instructions, see Section 5 of [Appendix 2](#)).

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

The following disease-related events are common in participants with cancer and can be serious/life-threatening:

- Progression of the underlying cancer (disease progression).

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE.

8.3.9 Management of Specific Adverse Events

Guidelines for the management of AEs associated with RO7300490 are provided in the subsections below. For the management of AEs specific to atezolizumab, see [Appendix 10](#) and the [atezolizumab Investigator's Brochure](#). For AEs related to both RO7300490 and atezolizumab, the management guidelines for RO7300490 should be used. For the management of AEs specific to tocilizumab, see Section [8.3.9.8](#), [Appendix 11](#), and the [tocilizumab Investigator's Brochure](#).

For cases in which management guidelines are not covered in this protocol or in the respective Investigator's Brochure, toxicities should be treated as deemed appropriate by the Investigator according to best medical judgment and local medical guidelines.

8.3.9.1 Management Guidelines for Infusion-Related Reaction/Cytokine-Release Syndrome

CRS is a supra-physiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. According to the definition provided by Lee et al. (2019), CRS must include fever at onset and may include hypotension and hypoxia. Additional signs and symptoms of CRS may include rigors, dyspnea, gastro-intestinal symptoms, cytopenias, coagulopathy with or without disseminated intravascular coagulation, and end organ dysfunction.

Neurologic symptoms may occur during or after the start of symptoms associated with CRS. When CRS is associated with T cell engaging bispecific antibody therapies (e.g., mosunetuzumab, glofitamab, cibisatamab), the time to CRS onset varies. CRS may occur during the infusion or within the first hours after the end of the infusion. The time to onset of CRS peaks at around 12 to 24 hours after the end of the infusion. In most cases, the clinical signs and symptoms of CRS are most severe with the first infusion; however, CRS may also occur with subsequent infusions. Late onset CRS has been observed in Roche studies, albeit infrequently. Two severe cases of ADA-mediated CRS were reported after five cycles of treatment with cibisatamab (dose increment approach).



The term “IRR” is used to describe systemic reactions following any type of IV therapy, including chemotherapy, monoclonal antibodies, and other biologics, which typically occur within 24 hours of study drug infusion, predominantly after the first infusion, with incidence and severity typically decreasing upon subsequent infusions. However, as IRRs may be indistinguishable from CRS based on the clinical signs and symptoms, an event with clinical presentation of CRS with onset within 24 hours from the end of

infusion of RO7300490 should be reported using the preferred term “cytokine release syndrome.” *If a participant experiences an isolated episode of fever during or within 24 hours after RO7300490 administration, and if it is judged to be related to study drug infusion, it should be reported as CRS.* If later in the study, there were evidence at the population level of cytokine-driven clinical signs and symptoms, and/or responsiveness to tocilizumab or other cytokine-directed therapies, it would be concluded that CRS was indeed present. Otherwise, retrospective recording to appropriate alternative diagnoses would be possible per Investigator judgment. The poorly defined terms such as “flu-like symptoms” or “systemic inflammatory response” must be avoided in conjunction with AEs related to RO7300490 administration.

Investigations, including IgE/tryptase levels and ADAs, should be performed to facilitate the distinction between IRR/CRS and hypersensitivity reactions. In some cases, IRR/CRS may be indistinguishable from an anaphylactic reaction. However, if elevated IgE and tryptase levels are consequently detected in blood samples of a participant who had signs and symptoms indicative of anaphylaxis or an anaphylactoid reaction, the participant is not to be re-challenged with RO7300490. The same would apply if there were a suspicion of anaphylaxis in the absence of laboratory findings, based on clinical assessment by the Investigator at the time of the finding. If a hypersensitivity reaction is induced by pADAs, it might be expected to result in a clinical pattern overlapping with that of CRS but with an early onset, potentially starting even during the infusion. Differential diagnosis is possible only via testing of ADAs. At the time of the event, full ADA characterization may not be feasible but the need for additional retrospective analysis will be explored.

During the initial cycles of treatment, intensive vital sign monitoring and laboratory analysis (biochemistry and hematology) will be conducted (refer to the SoAs in Section 1.3). Blood samples will be collected for central analysis of the cytokine panel as detailed in the SoAs. Additional and unscheduled blood samples should be taken at any time if signs and symptoms suggest a CRS event of Grade ≥ 3 for both local and central analyses as per SoAs (Section 1.3).

Clinical decisions should be based on the results of the following local analyses: hematology, blood chemistry, coagulation, and IgE/tryptase.

For a late onset CRS or CRS refractory to treatment, a differential diagnosis of HLH/MAS should be considered (Section 8.3.9.2).

Due to the significant overlap of signs and symptoms of IRR and CRS, consolidated treatment guidelines for IRR/CRS as well as recommendations for future RO7300490 administration(s) or RO7300490 discontinuation are provided in Table 13.

Severe *SARS-CoV-2 infection* is associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2 and IFN- γ . RO7300490 has a potential risk of CRS; therefore,

if a participant develops severe CRS during the study, a differential diagnosis, including testing to rule out *SARS-CoV-2* infection, should be considered.

Table 13 Principles for Management of IRR/CRS Related to RO7300490

CRS Grade ^a	Action with Current Infusion of RO7300490	Supportive Care	Corticosteroid Therapy/Anti-IL-6	Action for Next Dose of RO7300490
Grade 1 Fever ^b $\geq 38^{\circ}\text{C}$	<ul style="list-style-type: none"> Immediately interrupt infusion Upon symptoms resolution, restart infusion at (no more than) 50% starting rate If symptoms recur, discontinue infusion for this dose 	<ul style="list-style-type: none"> Supportive care^c for constitutional symptoms Maintenance IV fluids for hydration. Consider hospitalization until symptoms completely resolve 	<ul style="list-style-type: none"> Corticosteroids should be considered first line treatment unless there is clinical or biomarker evidence for use of tocilizumab before corticosteroids In case of rapid decline or prolonged CRS (>2 days) or in participants with significant symptoms and/or comorbidities (per Investigator discretion; e.g., impaired cardiovascular function, reduced pulmonary reserve), consider administration of IV corticosteroids and tocilizumab^d or another anti-cytokine agent 	<ul style="list-style-type: none"> Continue treatment with RO7300490 at the next scheduled dose administration Pre-medicate with acetaminophen and an antihistamine for all subsequent infusions Consider starting with the previous lower rate (the rate used after resolution of symptoms) for subsequent doses Consider hospitalization for next dose (in consultation with the Medical Monitor)
Grade 2 Fever ^b $\geq 38^{\circ}\text{C}$ with hypotension <u>not requiring</u> vasopressors and/or ^e	<ul style="list-style-type: none"> Immediately interrupt infusion Upon symptoms resolution, infusion may be restarted at (no more than) 50% starting rate If symptoms recur, discontinue infusion for this dose 	<ul style="list-style-type: none"> Follow recommendations for Grade 1 IRR/CRS Monitor cardiac and other organ functions closely (in ICU if appropriate); manage constitutional symptoms and organ toxicities as required <p>For hypotension:</p> <ul style="list-style-type: none"> IV fluid bolus 250–500 cc which may be repeated once based on 	<ul style="list-style-type: none"> Consider starting IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg IV every 6 hours) Corticosteroids should be considered first-line treatment unless there is clinical or biomarker evidence for use of anti-cytokine therapy before corticosteroids 	<ul style="list-style-type: none"> May receive the next dose of RO7300490 if symptoms resolve to Grade ≤ 1 for 3 consecutive days; the dose for the subsequent administration should be determined in consultation with the Medical Monitor

CRS Grade ^a	Action with Current Infusion of RO7300490	Supportive Care	Corticosteroid Therapy/Anti-IL-6	Action for Next Dose of RO7300490
hypoxia requiring <u>low-flow oxygen</u> ^f by nasal cannula or blow-by		<p>hemodynamic status per investigators clinical judgment</p> <ul style="list-style-type: none"> For refractory or unstable hypotension after at most two fluid boluses and anti-IL6 therapy, start vasopressors, and manage as Grade 3 IRR/CRS <p>For hypoxia:</p> <ul style="list-style-type: none"> Treat with low-flow oxygen^f Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours or atypical presentation, initiate workup and assess for signs and symptoms of HLH/MAS as described in Section 8.3.9.2. Hospitalization until complete resolution of signs/symptoms 	<ul style="list-style-type: none"> Administer tocilizumab^d or another anti-cytokine agent based on characterization of CRS Manage according to recommendations for Grade 3 IRR/CRS if no improvement within 8 to 12 hours after starting tocilizumab 	<ul style="list-style-type: none"> Administer pre-medications with acetaminophen and an antihistamine for all subsequent infusions Pretreatment with corticosteroids may be considered upon consultation with the Medical Monitor and in context of benefit/risk Consider starting with the previous lower rate (the rate used after resolution of symptoms) for subsequent doses Consider hospitalization for next dose (in consultation with the Medical Monitor) If symptoms recur despite pre-medications, with greater severity at subsequent cycles, the infusion should be stopped immediately and the participant permanently discontinued from study treatment

<p>Grade 3 Fever^b $\geq 38^{\circ}\text{C}$ with hypotension requiring a vasopressor (with or without vasopressin) and/or^e</p> <p>hypoxia requiring high flow oxygen^f by nasal cannula, face mask, non-rebreather mask, or Venturi mask</p>	<ul style="list-style-type: none"> • Immediately interrupt infusion • Upon symptoms resolution, do not restart infusion • Participants must be discontinued from study treatment if they experience Grade 3 wheezing, bronchospasm or generalized urticaria at first occurrence or if these symptoms recur 	<ul style="list-style-type: none"> • Follow recommendations for Grade 1 IRR/CRS • Recommend cardiopulmonary and organ function monitoring in the ICU; administer IV fluids as clinically indicated; closely monitor and maintain fluid balance • Manage organ toxicities symptomatically • For hypotension: <ul style="list-style-type: none"> • IV fluid bolus as described in Grade 2; vasopressor support at high and repeated doses as required • For hypoxia: <ul style="list-style-type: none"> • Treat with high-flow oxygen^f • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH/MAS (Section 8.3.9.2) • Hospitalization until complete resolution of signs/symptoms • Consider ruling out SARS CoV-2 infection 	<ul style="list-style-type: none"> • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg IV every 6 hours, unless clear evidence of CRS is present) • If clear evidence of CRS is present, administer tocilizumab^d or another anti-cytokine agent based on prior characterization of CRS • Manage according to recommendations for Grade 4 IRR/CRS if no improvement within 8–12 hours after second dose of tocilizumab 	<ul style="list-style-type: none"> • May receive the next dose of RO7300490 if symptoms resolve to Grade ≤ 1 for 3 consecutive days; consideration should be given to reducing the dose for subsequent administration upon consultation with the Medical Monitor • Administer pre-medications with acetaminophen and an antihistamine for all subsequent infusions • Pretreatment with corticosteroids may be considered upon consultation with the Medical Monitor and in context of benefit/risk • Consider starting with the previous lower rate (the rate used after resolution of symptoms) for subsequent doses • Consider hospitalization for next dose • If symptoms recur despite pre-medication, with same or greater severity at subsequent cycles, the infusion should be stopped
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CRS Grade ^a	Action with Current Infusion of RO7300490	Supportive Care	Corticosteroid Therapy/Anti-IL-6	Action for Next Dose of RO7300490
				immediately and the participant permanently discontinued from study treatment
Grade 4 Fever ^b $\geq 38^{\circ}\text{C}$ with hypotension requiring multiple vasopressors (excluding vasopressin) and/or ^e hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	<ul style="list-style-type: none"> Stop infusion Upon symptoms resolution, do not restart infusion 	<ul style="list-style-type: none"> Follow recommendations for Grade 3 IRR/CRS Participant requires ICU admission for hemodynamic monitoring, and/or mechanical ventilation, and/or IV fluids and vasopressors as needed 	<ul style="list-style-type: none"> Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/d or dexamethasone 10 mg IV every 6 hours) Administer tocilizumab^d or another anti-cytokine agent based on characterization of CRS For participants who are refractory to tocilizumab therapy, experimental therapies (e.g., siltuximab, anakinra, emapalumab^g, or LCK-inhibitors^g) may be considered at the discretion of the investigator. Management should be discussed with the Medical Monitor and consultation documented. 	<ul style="list-style-type: none"> In exceptional circumstances, may receive the next dose of RO7300490 dependent on, for example, participant's organ function/reserve, clinical benefit being derived, and level to which CRS has been characterized with RO7300490. This should be discussed with the Medical Monitor and the decision documented. If decision is made to administer the next dose: Administer pre-medications with acetaminophen and an antihistamine for all subsequent infusions Pretreat with corticosteroids in consultation with the Medical Monitor Consideration should be given to reducing the dose for subsequent administration in

CRS Grade ^a	Action with Current Infusion of RO7300490	Supportive Care	Corticosteroid Therapy/Anti-IL-6	Action for Next Dose of RO7300490
				<p>consultation with the Medical Monitor (Section 6.6)</p> <ul style="list-style-type: none"> Start with the previous lower rate (the rate used after resolution of symptoms) for subsequent doses Hospitalize for next dose If symptoms recur despite pre-medications, the infusion should be stopped immediately and the participant permanently discontinued from study treatment

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = Bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = Cytokine Release Syndrome; ICU = intensive care unit; IRR = infusion-related reaction; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SOA = schedule of assessment.

^a CRS grading per ASTCT ([Lee et al. 2019](#)).

^b Fever defined as temperature $\geq 38^{\circ}\text{C}$, not attributable to any other cause. In participants who develop CRS, and then receive antipyretic or anti-cytokine therapy (e.g., tocilizumab or steroids), fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

^c Participants should be treated with acetaminophen and an antihistamine (e.g., diphenhydramine), if they have not been administered in the previous 4 hours. For bronchospasm, urticaria, or dyspnea, treat per institutional practice. Treat fever and neutropenia as required; consider broad-spectrum antibiotics and/or granulocyte colony-stimulating factor, if indicated.

^d Tocilizumab should be administered as described in Section 6.1.3; refer to [Appendix 11](#) for SoA for tocilizumab treatment of CRS.

^e CRS grade is determined by the more severe event: hypotension or hypoxia, not attributable to any other cause.

^f Low-flow nasal cannula is defined as oxygen delivery at ≤ 6 L/min and may include blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

^g Reference: [Riegler et al. 2019](#); [Wu et al. 2019](#). The list of experimental therapies is not exhaustive and will evolve over time as new clinical trial data become available.

8.3.9.2 Management of Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

HLH is a severe hyperinflammatory syndrome induced by aberrantly activated macrophages and cytotoxic T cells. Clinical hallmarks of HLH include fever, hepatosplenomegaly, and cytopenias, combined with a characteristic set of laboratory parameters (elevated ferritin, triglycerides, soluble CD25, AST/ALT, lactate dehydrogenase [LDH], D-dimers; decreased fibrinogen, albumin, and sodium) ([Lehmberg et al. 2015](#)).

Proposed criteria for HLH have been published ([Hejblum et al. 2014](#), [Fardet et al. 2014](#)). Management of participants with HLH should be focused on the treatment of CRS. In “atypical” cases, such as late onset CRS or CRS that is refractory to treatment, workup for HLH/macrophage activation syndrome (MAS) should be initiated, and all cases of suspected HLH/MAS should be discussed with the Medical Monitor immediately.

A diagnosis of HLH/MAS should be suspected in participants who present with:

- Signs and symptoms of sepsis.
- Fever of unknown origin.
- Grade ≥ 3 CRS at onset.
- CRS signs and symptoms, regardless of severity, which present > 72 hours following the infusion of the study drug/molecule/product.
- CRS symptoms, regardless of severity, which persist for > 24 hours following initial management.

In all cases of suspected HLH/MAS, the Medical Monitor should be immediately notified and participants should be hospitalized.

Specific diagnostic criteria for HLH and MAS have been published, and they are presented in detail in [Appendix 10](#). In addition to obtaining the necessary clinical and laboratory assessments (e.g., splenic ultrasound) for the diagnosis of HLH/MAS, the following diagnostic and monitoring measures should be initiated at the time of hospitalization:

- Frequent vital signs and physical examination, including evaluation for splenomegaly.
- Serial (at least daily) monitoring of serum chemistries, complete blood counts, LFTs, ferritin, prothrombin time (PT)/partial thromboplastin time (PTT), fibrinogen, D-dimer, and triglycerides.
- Complete infectious disease workup, including:
 - Urine and blood cultures.
 - Urinalysis.
 - Radiographic assessments.

- Assessment for active viral infections, including, but not limited to, EBV (anti-EBV antibodies and EBV DNA by PCR), CMV, and HHV-6.
- Bone marrow and/or lymph node biopsy, if possible, to assess for hemophagocytosis and active infection, including assessment of the diagnosis of chronic active EBV infection via the localization of EBV probes (EBV-encoded RNAs/EBV-encoded nuclear antigen) in T/B/NK cells.
- If available, assessment of soluble CD25 and NK cell function.
- DNA for exploratory genetic testing of mutations potentially associated with HLH (e.g., PRF1, MUNC13-4, STXBP2) should be considered ([Zhang et al. 2011](#)). It is important to highlight that genetic testing may reveal variants of unknown significance and the clinical relevance of these results may be unknown.

In the setting of HLH/MAS with cancer immunotherapies, supportive and interventional care should follow the management guidelines described for CRS. Treatment options for cases of HLH/MAS, where anti-cytokine therapies (with or without high dose corticosteroids) fail to induce the desired response, will be based on published guidelines ([La Rosée 2015](#), [Schram and Berliner 2015](#), [Goldsmith et al. 2019](#)). Given that there is no SoC for HLH/MAS in these clinical situations, treatment in these cases must be discussed between the Sponsor and the Investigator on a case-by-case basis and documented. For more details, refer to [Appendix 10](#).

8.3.9.3 Management Guidelines for Immune-Mediated Adverse Events with RO7300490 or Atezolizumab

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

Although management varies according to the organ system affected, in general, RO7300490 therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities. RO7300490 therapy may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of RO7300490 and the initiation of high-dose corticosteroids (prednisone, 1 to 2 mg/kg/day, or methylprednisolone, 1 to 2 mg/kg/day). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy. In general, permanent discontinuation of RO7300490 is recommended with Grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement. Please refer to ASCO ([Puzanov et al. 2017](#)) and ESMO clinical practice guidelines for management of imAEs ([Haanen et al. 2017](#)).

The management guidelines for imAEs associated with RO7300490 or atezolizumab are provided in [Appendix 10](#). Samples to be collected in case of suspected imAE are detailed in the SoAs (Section [1.3](#)).

8.3.9.4 Management of Thrombocytopenia

- Participants should be closely monitored for blood platelet count.
- Platelet transfusion according to institutional practice will be at the discretion of the Investigator.
- Modifying the use of any concomitant therapies that may worsen thrombocytopenia-related events (such as platelet inhibitors and anticoagulants) should also be considered.
- Study-treatment interruption or permanent discontinuation should be discussed with the Medical Monitor in case of Grade 3 or 4 thrombocytopenia of any duration that is associated with Grade ≥ 3 bleeding and any consultation documented.

Actions to be taken with RO7300490 during study treatment are summarized in [Table 14](#).

Table 14 Management Guidelines for Thrombocytopenia with RO7300490

Event	Management
Thrombocytopenia, Grade 1 or 2	<ul style="list-style-type: none">• Withhold RO7300490 and consult with hematologist if thrombocytopenia Grade ≥ 2 continues for more than 7 days.
Thrombocytopenia, Grade 3 or 4	<ul style="list-style-type: none">• Withhold RO7300490 for a maximum of 3 weeks. Initiate supportive treatment.• Discontinue RO7300490 if no improvement to Grade ≤ 1 within 3 weeks.

8.3.9.5 Management of Thromboembolism and Coagulation Abnormalities

During treatment with RO7300490, coagulation parameters need to be monitored at screening and then on treatment using as a minimum PT, aPTT, INR, fibrinogen, and D-dimers. Thromboembolism while on treatment with RO7300490 should be managed according to the guidelines provided in [Table 15](#).

Table 15 Management Guidelines for Venous and Arterial Thromboembolic Events with RO7300490

Event	Management
Venous thromboembolic event, Grade 1 or 2	No study treatment modifications
Venous thromboembolic event, Grade ≥ 3	<ul style="list-style-type: none"> • Withhold RO7300490. Initiate supportive treatment. • Consider permanent discontinuation of RO7300490 after discussion with Medical Monitor.
Arterial thromboembolic event: New onset, worsening, or unstable angina pectoris, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event.	<ul style="list-style-type: none"> • Discontinue RO7300490.

8.3.9.6 Management of Tumor Inflammation/Tumor Flare

AEs associated with tumor inflammation have been reported with T cell-engaging therapies and are consistent with the mechanism of action leading to influx of T cells into tumor sites. Tumor flare may occur with a short time to onset following RO7300490 administration and may present with varying degrees of severity.

In addition, depending on tumor size and anatomic location, events associated with tumor inflammation/flare may potentially result in mass effects on vital structures, including airways, major blood vessels, and/or major organs.

The study Investigator should contact the Medical Monitor to discuss the benefit/risk, risk assessment, and mitigation strategies prior to enrollment and initiating RO7300490 treatment especially in participants with tumors involving critical anatomic locations. Such participants should be closely monitored for tumor inflammation and preventive or interventional measures may need to be considered or planned prior to dosing. Management guidelines are summarized in [Table 16](#).

Table 16 Management of Suspected Tumor Inflammation/Flare with RO7300490

Event	Initial Management Recommendation	Action to be Taken with RO7300490
Respiratory Toxicities		
Supportive measures, e.g., oxygen support and intubation, as indicated		
Grade 1	Monitor participant closely.	Continue treatment
Grade 2	Monitor participant closely If no resolution to Grade ≤ 1 within 48 hours, administer 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until Grade ≤ 1 .	Hold until resolution to Grade ≤ 1
Grade 3/4	Administer 2 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until resolution to Grade 1 or baseline. Ensure participant access to an intensive care unit is available.	Hold until resolution to Grade ≤ 1 Consider permanent discontinuation after discussion with Medical Monitor
Toxicities in Other Organ Systems		
Grade 1	Monitor participant closely.	Continue treatment
Grade 2	Monitor participant closely.	Hold until resolution to Grade 1
Grade 3	Administer 1 mg/kg/day of IV methylprednisolone or equivalent followed by tapering with oral steroids until Grade 1 or baseline (consider escalating next day to 2 mg/kg/day if no improvement or escalate to 2 mg/kg directly if event occurs during prophylactic treatment with steroids) Ensure participant access to an intensive care unit is available.	Hold until resolution to Grade ≤ 1 For Grade ≥ 3 toxicity and duration ≥ 5 days, consider permanent discontinuation after discussion with Medical Monitor
Grade 4	Administer 2 mg/kg/day of IV methylprednisolone or equivalent until Grade 1 or better. Ensure participant access to an intensive care unit is available.	Hold until resolution to Grade ≤ 1 . For Grade ≥ 3 toxicity and duration ≥ 5 days, consider permanent discontinuation after discussion with Medical Monitor

8.3.9.7 Management of Atezolizumab-Specific Adverse Events

For the complete information about management of toxicities related to atezolizumab, refer to the [atezolizumab Investigator's Brochure](#). Management guidelines for risks and atezolizumab-induced AEs, including pulmonary events, hepatic events, gastrointestinal events (diarrhea or colitis), endocrine events, ocular events, immune-mediated myocarditis, IRR/CRS, pancreatic events, dermatologic events, neurologic disorders, immune-mediated meningoencephalitis, renal events, immune-mediated myositis, and HLH, and MAS are provided in [Appendix 10](#).

8.3.9.8 Management of Adverse Events related to Tocilizumab

The following AEs are considered as important risks associated or potentially associated with chronic dosing of tocilizumab either as single agent or in combination with methotrexate or another disease-modifying anti-rheumatic drug in patients with

moderate to severe rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, polyarticular-course juvenile idiopathic arthritis, and giant cell arteritis:

- Serious infections,
- Complications of diverticulitis/gastrointestinal perforations and
- Serious hypersensitivity reactions including anaphylaxis, neutropenia, and hepatotoxicity.

Tocilizumab is used as a treatment for the management of CRS (Section 8.3.9.1) and not for long-term use; therefore, hypersensitivity reactions related to tocilizumab are considered the most relevant AE. Indeed, serious hypersensitivity reactions (including anaphylaxis) have been reported in association with infusions of tocilizumab; therefore, the participants being treated with tocilizumab for managing CRS should be closely monitored. If an anaphylactic or other serious hypersensitivity reaction occurs, administration of tocilizumab should be stopped immediately, and tocilizumab should be permanently discontinued.

For further information, see the [tocilizumab Investigator's Brochure](#).

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).

For this study, any dose of RO7300490 greater than 150% of the assigned dose level will be considered an overdose.

In the event of an overdose, the Investigator should:

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

The Sponsor does not recommend specific treatment for an overdose. 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.

8.5 PHARMACOKINETICS

The PK sampling schedule for RO7300490 is designed to provide a detailed profile of the concentration-time curve after IV administration and to provide appropriate exposure data for PK modelling and PK-ADA correlations. In addition, the PD sampling schedule is expected to provide dynamic information of the magnitude and kinetics of peripheral blood B cell depletion as a surrogate marker of B cell activation, and cytokine and chemokines/chemokine ligands release. This should enable analysis and understanding of the relationship between exposure and PD effects, and it may support PK- and/or PK/PD-based dose and schedule selection.

Mandatory blood samples to evaluate concentrations of study treatment will be collected from an IV line placed in the arm opposite to that used for study treatment administration, and will be processed to serum. The blood samples for RO7300490 PK will be collected as outlined in the SoAs (Section 1.3). In addition, in Part 2 only, dedicated blood samples will be used for confirming the exposure of atezolizumab as described in the SoA. If tocilizumab is used, the blood samples needed to determine tocilizumab concentrations, will be collected at the time points indicated in the SoA for tocilizumab (Appendix 11). The date and time of each sample collection will be recorded in the eCRF.

RO7300490 concentrations in serum will be analyzed with a validated bioanalytical electrochemiluminescent assay (dual binding competent assay). In addition, to support future PK/PD analysis and potential modeling, an exploratory assessment of RO7300490 uptake and dynamic tumor (target site) is planned to be conducted using imaging technologies (imaging sub-study) as described in Section 4.1.

During the course of the study, the PK sampling time points may be modified based on emerging data to ensure optimal characterization of RO7300490 PK and disposition without increasing the overall blood collection volume.

Additional (unscheduled) RO7300490 blood PK samples will be taken:

- If the participant experiences Grade ≥ 3 IRR/CRS or Grade ≥ 3 hypersensitivity reaction (Section 8.3.9).
- If the participant experiences a RO7300490-related \geq Grade 2 AE leading to delay and/ or discontinuation of RO7300490 administration (Section 6.6).
- In case of overdose during a cycle when a PK sample is not collected as per SoAs (Section 1.3).

Any volume of blood remaining after the specified analyses may also be used for further characterization of immune responses and for any RO7300490-related exploratory analyses or any assay development or validation experiments.

The PK blood samples will be destroyed at the latest 2 years after the date of final clinical study report unless the participant gives specific consent for the remainder of the sample(s) to be used for optional exploratory research within the RBR. Details on sampling procedures, sample storage, and shipment are given in the Sample Laboratory Flow Chart.

8.6 IMMUNOGENICITY RISKS AND ASSESSMENTS

As RO7300490 is a human antibody, there is a risk that ADA against this molecule will develop, potentially reducing its efficacy and/or potentially resulting in symptomatic hypersensitivity reaction, in particular immune-complex reactions.

In addition, based on non-clinical immune-safety studies, the clinical immunogenicity profile of RO7300490 might be exacerbated by the specific RO7300490 MoA, which by stimulating the CD40 receptor in FAP expressing tissues including lymph nodes, indirectly activates immune-responses (for more information on MoA and immune-safety assessment, refer to the [RO7300490 Investigator's Brochure](#)).

These drug-reactive antibodies, commonly named as “pre-existing antibodies,” are frequently present in human without prior drug exposure and have been previously described ([Xue et al. 2017](#)). They are components of the human autoantibody or cross-reactive antibody repertoire and may or may not be boosted upon exposure to RO7300490. Clinical consequences of these pADA for RO7300490 cannot be anticipated by preclinical studies and can vary from no effects to adverse effects on patient safety (e.g. IRR/CRS risks), reduced drug exposure and efficacy, and are expected to be highly dependent on biotherapeutic modality, disease indications, and patient demographics.

In Study WP42627, ADAs to RO7300490 will be evaluated in blood samples collected from all participants pre- and post-treatment, at treatment discontinuation and safety follow-up, according to the SoAs (Section 1.3). Additional ADA samples should also be collected in participants who experience a Grade ≥ 3 IRR/CRS or Grade ≥ 3 hypersensitivity reaction, in particular immune-complex reaction, *or RO7300490-related Grade ≥ 2 AE leading to treatment interruption/discontinuation or delay*. In each case, for each collected ADA sample, a corresponding PK sample will be collected at the same time point for the determination of RO7300490 concentration. The date and time of each sample will be recorded in the eCRF.

Validated screening, confirmatory, and titer assays will be employed to analyze the presence of ADAs against RO7300490. Depending on the emerging results of the study, leftover serum samples might be used for performing additional quantifications with different methodologies to better understand the effect of the body on the PK of the

studied drug. Similarly, the leftover serum samples might be used to better characterize the ADA, for example to understand where they bind on the drug and if they block its efficacy.

In addition, dedicated blood samples will be used for the determination of ADAs against atezolizumab (Part 2 only). When tocilizumab is used, blood samples to determine the presence of ADAs against tocilizumab will also be collected (Section 1.3 and tocilizumab SoA in [Appendix 11](#)).

Leftover blood samples from ADA analyses will be destroyed at the latest 2 years after the date of final clinical study report, unless the participant gives specific consent for the remainder of the sample(s) to be used for optional exploratory research within the RBR.

Details on sampling procedures, sample storage, and shipment are described in separate sample handling documentation.

8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

Peripheral blood and tumor tissue samples will be tested for protein, nucleic acid, or other tissue or blood derived biomarkers relating to the proposed MoA of RO7300490. These include, but are not limited to:

- Drug CD40 receptor occupancy on B cells in blood.
- Cellular profile in blood and tissue.
- Cytokines and other soluble markers of inflammation in blood and tissue.
- Biomarker assessments in paired tumor tissue such as APC or T cell subset function or activation status.

■ [REDACTED]

For further considerations, refer to Section 4.2.2. Additional markers may be measured if a strong scientific rationale develops. Note that as science and research are evolving, the list of biomarkers that will be evaluated cannot be fully defined.

8.7.1 Genetic and Genomic Analyses **Transcriptome Analysis**

Tumor biopsy material will be used for RNA extraction and subsequent gene expression profiling to enable:

- Identification of pharmacodynamics biomarkers.
- Identification of response predictive biomarker.
- Assessment of treatment response and/or MoA (in terms of pharmacodynamics).

8.8 PHARMACODYNAMICS AND BIOMARKER SAMPLES

Blood and tissue samples will be collected as specified in the SoAs (Section 1.3). The date and time of each sample collection will be recorded in the eCRF. Details on processes for collection and shipment of these samples can be found in the Laboratory Flow Chart.

Based on the continuous analysis of the data derived from Study WP42627 and other studies, the collection of any sample type and/or any analysis not considered critical for safety or biomarker assessment may be stopped at any time if the data from the upcoming samples collection will not provide additional valuable information.

Any collected sample remaining after the specified analyses (Section 8.7) may be used for additional (assay) validation experiments. Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to RO7300490.

Residual plasma/serum samples (collected for PD/biomarker research or PK/ADA testing) may also be used for longitudinal testing of bacterial or viral infection (e.g., SARS-CoV-2) by serological methods. This testing may be performed for each participant. In addition to serving as an important safety measure, these analyses will inform as to any association of bacterial or viral infection and response to treatment.

Unless otherwise specified below, PD and biomarker samples (including whole blood, plasma, tissue, cell pellets, slides, extracts, etc.) will be destroyed no later than 5 years after the date of final clinical study report. For participants who consent to RBR, leftover samples will be transferred to the RBR (Section 8.9).

8.8.1 Samples

Blood and tumor tissue samples for PD and biomarker research will be collected from study participants at the time-points described in the SoAs (Section 1.3).

8.8.1.1 Blood Sampling

The following samples are mandatory and will be collected from all participants enrolled in Part 1 and Part 2, *except from the participants who transferred from the imaging sub-study WP42627/IMG*:

- Blood samples for the measurement of receptor occupancy.
- Blood samples for the measurement of cytokines/chemokines (e.g., IP-10, IL-6, IL-8) and immune activation markers such as sCD25.
- Blood samples for the flow cytometry analysis of changes in the numbers of lymphocyte subsets including but not limited to B cells, T cells and NK cells.

Collection of peripheral blood samples for the purposes as described in this section within Part 3 of the study will be dependent on emerging data justifying the requirement for continued assessment of the respective biomarkers.

8.8.1.2 Tumor Tissue Sampling

Archival Tumor Samples

For all participants in Part 1 and Part 2, [REDACTED] as well as for all participants in Part 3, [REDACTED] when available *and must be considered after eligibility is confirmed, if possible.*

Archival tumor tissue sample should have been obtained less than 12 months prior to RO7300490 treatment. The primary tumor and the most recent metastasis (if both are available) should be submitted for analysis. Ideally, these samples should include the invasive margin. Tumor blocks are preferred, but slides will be accepted.

Samples will be analyzed by immunohistochemistry (such as, but not limited to, CD8/MHC I/FAP) and immunofluorescence (such as, but not limited to, activation assessment of antigen-presenting cells).

For participants who will be enrolled in the study, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. In the event that the treating hospital or the Investigator do not wish to receive the remaining archival tissue blocks, they will be destroyed within 5 years after the date of final clinical study report. For participants who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

Fresh Tumor Biopsies

For all participants in Part 1 and Part 2, [REDACTED] collection of screening and on-treatment biopsies are mandatory. For Part 3, [REDACTED]

Fresh biopsies at screening must be obtained within 28 days before the first study treatment dose on C1D1. The screening biopsy should be collected after eligibility is confirmed, if possible. In the event that a fresh biopsy is taken during the screening period and the participant is not enrolled into the study, the sample can be returned to the site upon site request.

Existing biopsies available at the sites prior to the participant's entry in the study as a substitute to collecting a fresh study biopsy should be discussed with the Sponsor (i.e., biopsy should have recently been obtained as part of a diagnostic biopsy and participants should have not received any tumor treatment after this collection).

In order to mitigate the potential risk associated with tumor biopsies, all participants required to have a biopsy must have tumor lesions from which biopsies can be safely obtained, as per clinical judgment of the Investigator. The tumor lesion should not be a metastatic lymph node; a metastatic lymph node sample is acceptable only when other accessible tumor sites are not available for biopsy. If fresh tissue biopsies cannot be obtained, please contact the Medical Monitor.

Collection of tumor biopsies should be guided by ultrasound, CT scan, or other methods according to the location of the selected lesion, ideally using a 16- to 18-gauge needle to provide cores. An alternative needle size may be used following discussion with and documented consultation with the Sponsor. At least 2, ideally 3 core biopsies will be obtained at each timepoint (at the physician's discretion). Fine-needle aspiration, bronchoscopy/trans-bronchial biopsies, cytology, or biopsy of bone lesions are not acceptable.

If feasible, on-treatment biopsies may be repeated if the initial biopsy did not contain sufficient tumor material for analysis. The location of each biopsy will be documented in relation to each tumor lesion as determined by imaging. The screening and on-treatment biopsies should be preferably taken from the same tumor lesion (metastasis) to ensure comparability. If the sample cannot be collected from the same lesion (e.g., lesion disappears after treatment) then the on-treatment biopsy should preferably be collected from the same organ, if possible. Ideally, these samples should include the invasive margin and exclude necrotic zones.

Additional (optional) biopsy at time of PR, SD, progressive disease or any other time point of interest based on the participant's course of disease may be acquired after discussion between the Investigator and the Sponsor, and upon participant's consent. The Sponsor will continuously assess the need for making the biopsies mandatory.

Samples will be assessed by immunohistochemistry (such as, but not limited to, CD8/MHC I/FAP), immunofluorescence (such as, but not limited to assessment of APCs activation), and gene expression. It is also considered to include [REDACTED]

[REDACTED] This will be further defined with an amendment to this protocol.

8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.9.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from participants who give specific consent to participate in this optional RBR *and, if possible, when enrolment in the study is confirmed*. Collected RBR samples will be used to achieve the following objectives:

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

8.9.1.1 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7300490, diseases or drug safety:

- RBR blood sample.
- Leftover plasma samples.
- Leftover serum samples.
- Leftover tumor tissue samples (and any derivatives).

Samples 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 may be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

The repository samples will be subject to the confidentiality standards (as described under Confidentiality 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 pre-treatment assessments will be performed within 28 days prior to C1D1, unless otherwise specified. Results of SoC tests or examinations performed prior to obtaining informed consent and within 28 days prior to C1D1 may be used (and do not need to be repeated for screening).

8.11.2 Assessments at Scheduled Visits during Treatment

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

Exceptional measures during the COVID-19 pandemic, such as adjustments in study visits, may be considered (see Section 8.11.6).

8.11.3 Assessments at Unscheduled Visits

If clinically indicated, any assessment or sample specified in the SoAs (Section 1.3) can be performed any time as unscheduled assessment or sample at the discretion of the Investigator. Unscheduled eCRFs will be used to record any assessments performed during an unscheduled visit.

8.11.4 Assessments at Study Completion/Early Termination Visit

Participants who complete the study or discontinue from the study early will be asked to return to the clinic within 30 days after the final dose of study treatment for an EoT visit (SoAs in Section 1.3). The visit at which response assessment shows progressive disease, or at which the participant is discontinued or withdraws from the study may be used as EoT visit.

8.11.5 Follow-Up Assessments

Participants will be asked to return to the clinic 60 days (± 7 days) following last study treatment dose for a safety follow-up visit, unless they have withdrawn consent. Three-monthly (± 14 days) survival follow-up assessments will be performed on the phone. Refer to SoAs in Section 1.3.

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

8.11.6 Exceptional Measures during COVID-19 Pandemic

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.
- Temporary suspension of sample collection.

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.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Not applicable.

9.2 SAMPLE SIZE DETERMINATION

It is anticipated that at most 280 evaluable participants will be enrolled in Parts 1, 2, and 3 of this study.

The exact sample size in Part 1 (dose-escalation of RO7300490 as a single agent) and Part 2 (dose-escalation of RO7300490 in combination with atezolizumab) of the study will depend on the number of cohorts needed to reach the MTD and/or RDE. According to the mCRM-EWOC design, each part may require at most 60 participants for the dose-escalation ([Appendix 6](#)).

An analysis of RO7300490 effects in the tumor microenvironment is an important endpoint for demonstrating PD MoA in this study. This analysis will require paired tumor biopsies prior to and following RO7300490 dosing, as single agent or in combination with atezolizumab, for each participant in Part 1 and Part 2, [REDACTED]

[REDACTED] Participants with both tumor biopsy samples available and evaluable will be considered for exploratory PD objectives. To ensure sufficient data is collected for the analysis, the design for the Part 1 extension cohorts specifies approximately [REDACTED]

[REDACTED] 40 participants may be enrolled in the Part 1 extension cohorts.

Part 3 (dose-expansion of RO7300490 in combination with atezolizumab) is planned to have [REDACTED]

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in [Table 17](#).

Table 17 Analysis Populations

Population	Description
Efficacy	All participants enrolled in study WP42627, including those from the imaging sub-study, who received at least one dose of RO7300490 (as a single agent or in combination with atezolizumab) and who have at least one post-baseline tumor assessment and/or have discontinued the study due to clinical progression before the first on-study tumor assessment, will be included in the efficacy analysis.
Per protocol	A per protocol population may be advised for proof of concept or proof of mechanism studies and exclude, e.g., major protocol violators etc. A per protocol population for statistical analysis may only add value if it can be defined in a way so it may be more likely for the drug to show its effect.
Safety	All participants enrolled in study WP42627, as well as those participants transferred from the imaging sub-study, who received at least one dose of the study treatment (RO7300490 or atezolizumab or both) whether prematurely withdrawn from the study or not, will be included in the safety analysis.
Pharmacokinetic	All participants in the safety population who have PK 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 from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented with the reason for exclusion.
Immunogenicity	All participants with at least one ADA assessment, irrespective of whether the participant receives any treatment (Shankar et al. 2014).
DLT evaluable	DLT-evaluable participants are those who have completed the DLT-assessment window without DLT or those for whom a DLT is reported during the assessment window. This population will be used in the determination of the MTD and/or RDE.

9.4 STATISTICAL ANALYSES

The data will be analyzed by the Sponsor and/or designated Contract Research Organization. Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK and biomarker measurements. Data will be summarized by cohort and regimen within each part. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

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 cohort and regimen within each part.

9.4.2 Efficacy Analyses

The primary and secondary efficacy analyses listed in [Table 18](#) will include all participants in the efficacy population with participants grouped according to dose cohort and regimen within each study part. Primary, secondary, and exploratory endpoints are described in [Section 3](#).

Table 18 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
<ul style="list-style-type: none">• Objective response rate (ORR)• Disease control rate (DCR)• Duration of response (DoR)• Progression-free survival (PFS) According to RECIST Version 1.1	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 (NE) 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. DoR and PFS (on-treatment) will be summarized by using time-to-event analyses and Kaplan-Meier curves.
Overall Survival (OS)	OS data may be tabulated and summarized using time-to-event analyses and Kaplan-Meier curves if data is collected and mature. Summaries will be carried out by cohort (and schedule if applicable) separately for each part. This will be carried out for RECIST v1.1, and iRECIST efficacy endpoints in exploratory analysis.

Objective response rate (ORR) is determined as the rate of participants with an overall response of complete response (CR) or partial response (PR) as determined by the Investigator per RECIST v1.1. Disease control rate (DCR) is determined as the rate of participants with an overall response of either CR, PR, or stable disease (SD) rate. To classify a response as SD, measurements will have to be classified as stable (as determined by the Investigator according to RECIST v1.1) at least once after study entry at a minimum of 6 weeks after study entry. Objective response (OR) is defined as a CR or PR as determined by the Investigator. Participants with missing or no response assessments will be classified as not evaluable (NE) unless there is documented clinical deterioration, in which case participant will be classified as non-responders.

Duration of response (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 (PFS; on-treatment).

PFS on treatment will be defined as the time from study treatment initiation (C1D1) to the first occurrence of documented disease progression (per RECIST v1.1 Investigator's assessment) or death from any cause, whichever occurs first.

For participants who do not have documented progressive disease or death (within 30 days from last study treatment) during the study, PFS will be censored at the day of the last tumor assessment. Participants without any post-baseline assessments or with all post-baseline assessments having unknown result/response but known to be alive at the clinical cut-off for the analysis will be censored at the date of study treatment initiation plus one day.

Sensitivity analyses of response endpoints (ORR, DCR, DoR, and PFS) may include the evaluation of response according to iRECIST. As a sensitivity analysis, the analysis described in [Table 18](#) 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, the safety population will be the default analysis set used for all analyses. All safety analyses will be based on the safety analysis population grouped according to the treatment assigned. In case of parallel treatments available, then the analyses will be based on the treatment assigned at randomization. The safety endpoints and appropriate analyses are summarized in [Table 19](#).

Table 19 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Incidence, nature, and severity of AEs	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. AEs will be summarized by mapped term and appropriate thesaurus level, and NCI CTCAE v5.0 toxicity grade, with the exception of grading for CRS. For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF. AEs will be graded according to guidelines provided in Table 1 of Appendix 2 . All collected AE data will be listed by assigned dose level and participant number for each part of the study. Additionally, AEs that are attributed to RO7300490 or atezolizumab will be summarized in two separate tables through the same mapping or grading method. Glossary of AEs, medication, and procedures will be provided. In addition, all SAEs, including deaths, will be listed separately and summarized. DLTs and AEs leading to treatment discontinuation will also be separately listed. Individual and mean serum RO7300490 or atezolizumab concentration versus time data will be tabulated and plotted by dose level.
Nature and frequency of DLTs	DLT events will be presented by individual listings. The MTD will be estimated with an mCRM-EWOC model using DLT-evaluable participants. The MTD estimate will be presented along with 90% credible intervals.

Endpoint	Statistical Analysis Methods
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; <i>Système International d'Unités</i>) by individual listings with flagging of abnormal results. Summary tables of change from baseline over time will be displayed. Shifts in NCI CTCAE grades v5.0 from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. For details on standard reference ranges, data transformation, and the definition of laboratory abnormalities, see Appendix 4 .
Vital signs	Vital sign 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.

9.4.4 **Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Relationships Analyses**

Analyses will be carried out on the PK analysis population. Individual and mean serum RO7300490, atezolizumab, and tocilizumab concentration versus time data will be tabulated and plotted by dose level, and/or by dosing regimens, as appropriate.

When data allow, PK parameters will be derived from the serum concentrations of RO7300490 using standard non-compartmental methods, including but not limited to:

- Total serum exposure AUC.
- Time to maximum concentration observed in serum (t_{max}).
- Maximum (C_{max}) and minimum (C_{min}) concentration observed in serum during Cycle 1 (step-up dosing).
- Maximum and minimum concentration observed in serum under steady-state conditions within a dosing interval.
- Clearance (CL).
- Volume of distribution at steady-state (V_{ss}).
- Terminal half-life ($t_{1/2}$).

All PK parameters will be presented by listings and descriptive summary statistics by dose level, and/or by dosing regimens.

Further data analysis to estimate the dose-exposure relationships and the potential effect of target-mediated drug disposition and of ADAs on RO7300490 PK will be also conducted as appropriate.

Calculations of additional PK parameters and popPK analysis of RO7300490, atezolizumab, and tocilizumab will be performed as data allow. For RO7300490, population and individual PK parameters will be estimated, and the influence of various covariates (such as age, sex, and body weight) on these parameters will be investigated in an exploratory way. A previously developed model for atezolizumab PK will be used to provide individual parameter estimates using Bayesian feedback methodology, as appropriate and if required. Secondary PK parameters (such as C_{\max} and AUC) may be derived from the model for each individual included in the PK analysis and will be presented descriptively.

In addition, exploratory analysis of the dynamic relationships between exposure (PK) and PD markers, and safety and clinical activity data potentially emerging from the dose-escalation study will be conducted, as data allow, to inform the design and administration route(s) of the subsequent dose expansion phase.

The details of the popPK, PK/PD modeling results and any other exploratory data analyses will be reported in documents separate from the clinical study report.

9.4.5 Immunogenicity Analyses

Analyses will be carried out on the immunogenicity analysis population.

The number and proportion of ADA-positive and ADA-negative participants at baseline (baseline prevalence) and after study drug administration (post-baseline incidence during both the treatment and follow-up periods) will be summarized by dose level and/or dosing regimens, as appropriate, for RO7300490, atezolizumab, and tocilizumab.

Participants are considered “on-treatment ADA-positive” if:

- They are negative at baseline, or have missing data at baseline and develop an ADA response following study drug administration (treatment-induced ADA response), or
- They are ADA-positive at baseline (e.g. because of pADA cross-reactivity with RO7300490; see Section 8.6) and the ADA titer of one or more post-baseline samples is greater than the pADA titer of the baseline sample by at least 4-fold (treatment-enhanced ADA response).

Treatment-induced ADA responses will be further categorized as either:

- Transient ADA response defined as a) ADA-negative or missing data at baseline, and b) at least one post-treatment ADA-positive sample, and c) only one ADA-positive sample or the time between the first and last ADA-positive sample is less than 16-weeks, and d) the last ADA sample is negative.
- Persistent ADA response defined as a) ADA-negative or missing data at baseline and b) post-treatment ADA-positive samples over 16 weeks or more or the last ADA time point is positive (Shankar et al. 2014).

Participants are considered “on-treatment ADA-negative” if:

- They are ADA-negative at baseline or have missing data at baseline and all post-baseline samples are negative, or
- They are ADA-positive at baseline (pADA positive) and do not have any post-baseline samples with a titer that is greater than the pADA titer of the baseline sample by at least 4-fold (treatment unaffected).

The relationship between pADA and ADA status and/or ADA titers, and safety, efficacy, PK, and biomarker endpoints may be analyzed. The details of these analyses may be reported in a document separate from the clinical study report.

9.4.6 Pharmacodynamic Analyses

All PD parameters will be presented by listings and descriptive summary statistics separately by group or cohorts.

9.5 INTERIM ANALYSES

No formal interim analyses are planned during dose-escalation (Parts 1 and 2). Participant's safety will be reviewed on an ongoing basis and formally discussed between Sponsor and Investigators (Section [4.1.5](#)).

At the discretion of the Sponsor, non-binding interim analyses for safety and futility may be performed during Part 3 of the study. The first interim analysis per cohort may occur

[REDACTED]

At each interim analysis, the Sponsor and the Investigators will review the response data and decide whether to recommend an early decision to stop enrollment in the subgroup due to futility. Additional analyses may be conducted in order to guide early stopping of enrollment for safety based on observed toxicities.

9.6 SUMMARIES OF CONDUCT OF STUDY

All reportable protocol deviations will be listed.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

This section includes the following appendices:

[Appendix 1](#): Regulatory, ethical and study oversight

[Appendix 2](#): Adverse event definitions, follow-up, and reporting

[Appendix 3](#): Procedures for recording adverse events

[Appendix 4](#): Clinical laboratory tests

[Appendix 5](#): Contraceptive guidance and collection of pregnancy information

[Appendix 6](#): Statistical model dose evaluation

[Appendix 7](#): Modified RECIST v1.1 for immune-based therapeutics (iRECIST)

[Appendix 8](#): New response evaluation criteria in solid tumors version 1.1 modified excerpt from original publication with addition of supplementary explanations

[Appendix 9](#): ASTCT cytokine-release syndrome consensus grading

[Appendix 10](#): Management guidelines for immune-mediated adverse events associated with RO7300490 and/or combination therapy with RO7300490 and atezolizumab

[Appendix 11](#): Schedule of assessment for tocilizumab for cytokine-release syndrome

Appendix 1

Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

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

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. The Principal Investigator or delegate (referred to as Investigators in the protocol) 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. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

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

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

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

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

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

Participants who are re-screened and participants who are transferred from the imaging sub-study into the WP42627 main study are required to sign the study ICF.

Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their samples at any time and for any reason during the storage period. A separate, specific signature will be required to

document a participant's agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

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

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

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

Approval by the Institutional Review Board or Ethics Committee

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

Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the study is closed. A participant's withdrawal from Study WP42627 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 WP42627. Data already generated before time of withdrawal of consent to RBR will still be used.

1.4. CONFIDENTIALITY

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

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

Confidentiality for Research Biosample Repository

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

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

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

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

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

Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the ICF. The Sponsor's monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (see definition of end of study in Section 4.4 of the protocol).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

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

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

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that

the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.2. Clinical Outcome Assessment Data

Not applicable.

2.1.3. Source Data Records

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

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

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

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

2.1.4. Use of Computerized Systems

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

2.1.5. Safety Biomarker Data

Adverse event (AE) reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for

this study. In addition, safety biomarker data will not inform decisions on participant management.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period, the documents may be destroyed, subject to local regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

2.3. STUDY RECORDS

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

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

2.3.1. Protocol Amendments

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

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

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally

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

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

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

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

2.3.3. Dissemination of Clinical Study Data

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see confidentiality in Section 1.4 of this appendix), and redacted clinical study reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

2.3.4. Management of Study Quality

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

2.3.5. Site Inspections

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

3. ADMINISTRATIVE STRUCTURE

No formal independent review committee, independent data monitoring committee, internal monitoring committee or clinical events committee are planned for this study.

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

1. DEFINITION OF ADVERSE EVENTS

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

An adverse event can therefore be:

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

Events Meeting the AE Definition:

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

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious AE (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An 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, which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see [Appendix 3](#)).

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

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

Disability means substantial disruption of the participant's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect.**

- **Other significant events:**
- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

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

There may be instances when copies of medical records for certain cases are requested by 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]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity, *with the exception of CRS which will use the ASTCT Cytokine Release Syndrome Consensus Grading*. [Table 1](#) will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale

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

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

Note: Based on the NCI CTCAE (v5.0), which can be found at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

- ^a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- ^b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.
- ^c If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 6 of this Appendix for reporting instructions), per the definition of serious adverse event in Section 2.
- ^d Grade 4 and 5 events must be reported as serious adverse events (see Section 6 for reporting instructions), per the definition of serious adverse event in Section 2. Grade 4 laboratory abnormalities would only be reported as SAEs if these meets one or more of the conditions outlined in Section 2 (Definition of SAEs) of this appendix.

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 the Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor 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:

- SAE.
- Non-serious adverse events of special interest (NSAESI).
- Pregnancies (protocol Section 8.3.5).
- DLTs during the DLT assessment window (see Section 4.1.3.1; see the eCRF completion guideline for further guidance. For reporting purposes, the tick box "DLT" should be completed for events considered to contribute to the stopping criteria of the study (see protocol Section 4.1.4).

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

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

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

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

Events that Occur prior to Study Treatment Initiation

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

Events that Occur after Study Treatment Initiation

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

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

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

Reporting of Post-Study Adverse Events and Serious Adverse Events

After the end of the AE reporting period (see Section 8.3.1) after the final dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the Investigator becomes aware of a SAE that is believed to be related to prior study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to investigators.

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
- In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For RO7300490, atezolizumab, and tocilizumab, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with RO7300490, atezolizumab, and tocilizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong

dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

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

The Sponsor will promptly evaluate all 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 through use of the reference safety information in the documents listed below:

Drug	Document
RO7300490	RO7300490 Investigator's Brochure
RO7300490 plus atezolizumab in combination	RO7300490 Investigator's Brochure Atezolizumab Investigator's Brochure
Atezolizumab	Atezolizumab Investigator's Brochure
Tocilizumab	Tocilizumab Investigator's Brochure

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

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

Appendix 3

Procedures for Recording Adverse Events

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

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

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION-RELATED REACTIONS

AEs that occur during or after study drug administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., cytokine-release syndrome, infusion-related reaction (see Section 8.3.9.1 of the protocol) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction.” Associated signs and symptoms should be recorded on the dedicated Cytokine Release Syndrome, or 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 eCRF.

1.2. OTHER ADVERSE EVENTS

For AEs 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 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

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

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

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

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

4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE 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 AE.

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 AE. 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 AE. A vital sign result should be reported as an AE 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 AE.

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

For participants without liver metastases, the finding of an elevated ALT or AST ($\geq 3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($> 2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $\geq 3 \times \text{ULN}$ in combination with total bilirubin $> 2 \times \text{ULN}$.
- Treatment-emergent ALT or AST $\geq 3 \times \text{ULN}$ in combination with clinical jaundice.

For participants with cancer who have liver metastases or hepatocellular carcinoma or are receiving hepatotoxic concomitant medications, the finding of an elevated ALT or AST in combination with either an elevated total bilirubin or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of potential severe liver injury. Therefore, Investigators must report the occurrence of either of the following as an AE:

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

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

7. DEATHS

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

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

8. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept

that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

9. LACK OF EFFICACY OR WORSENING OF THE UNDERLYING DISEASE

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 Response Evaluation Criteria in Solid Tumors (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 AE.

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in [Appendix 2](#)), except as outlined below.

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

- 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 AE.

- Hospitalization due solely to progression of the underlying cancer.

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

- Hospitalization for an AE 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. The results of each test must be captured in source documentation and entered into the eCRF. Investigators must document their review of each laboratory safety report.

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

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

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

- In the event the local laboratory cannot perform auto-antibody testing, this may be analyzed centrally.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	<ul style="list-style-type: none"> Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
Clinical Chemistry	<ul style="list-style-type: none"> Sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, urea or blood urea nitrogen (BUN), creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH, CRCL^a, GGT, CRP, ferritin.
Coagulation	<ul style="list-style-type: none"> INR or prothrombin time (PT), activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT), fibrinogen. In case of abnormalities in INR, PT and/or aPTT, additional coagulation parameters (i.e., anti-thrombin III, fibrin degradation products, D-dimer) may be assessed according to clinical judgement and local site practices.
Viral Serology	<ul style="list-style-type: none"> 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. Polymerase chain reaction (PCR) for HBV and/or HCV RNA in case of positive antibody result.
Lipids	<ul style="list-style-type: none"> Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.
Thyroid hormones	<ul style="list-style-type: none"> TSH, free or total T3, free T4.
Pregnancy test	<ul style="list-style-type: none"> All women of childbearing potential (including those who have had a tubal occlusion/ ligation) will have a blood human chorionic gonadotropin (HCG) pregnancy test at screening. Urine pregnancy tests will be performed during study treatment. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.
IgE and tryptase	<ul style="list-style-type: none"> Tryptase and IgE samples will be collected for local analysis if a participant experiences a Grade ≥ 3 IRR/CRS or a Grade ≥ 2 hypersensitivity reaction. A second sample should be collected approximately 48 hours after onset of the reaction to rule out the possibility of an anaphylactic reaction.
Auto-antibodies	<ul style="list-style-type: none"> Anti-nuclear antibody (ANA), anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody (cANCA), and perinuclear anti-neutrophil cytoplasmic antibody (pANCA).
Urinalysis	<ul style="list-style-type: none"> Specific gravity. Dipstick: pH, glucose, protein or albumin, blood, ketones, bilirubin. If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture. Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) or urine culture (depending on local laboratory guidelines) is to be performed if blood or protein is abnormal.

^a CRCL= $\frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{SCr}} \times 0.85$ (if female); CRCL (creatinine clearance) = mL/minute; age = years; weight = kg; SCr (serum creatinine) = mg/dL.

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

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

Appendix 5

Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

- **Women 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 Women 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 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](#).

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)	
<ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: <ul style="list-style-type: none"> ○ Oral ○ Intravaginal ○ Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: <ul style="list-style-type: none"> ○ Oral ○ Injectable 	
Highly Effective Methods That Are User-Independent (Failure rate of < 1% per year)	
<ul style="list-style-type: none"> • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation^a • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion/ ligation <p>Vasectomized partner</p> <p>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.</p> <p>Sexual abstinence</p> <p>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.</p>	

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

3. **PREGNANCY TESTING**

For WOCBP enrolled in the study, serum and urine pregnancy tests will be performed according to the SoA tables (Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (which should be performed with leftover from clinical chemistry sample, if possible).

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

- **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 *Clinical Trial Pregnancy Reporting 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 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 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 and be withdrawn from the study.

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

- **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 study treatment.

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.

5 ABORTIONS

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

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

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

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

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

Appendix 6

Statistical Model Dose Evaluation

This appendix provides details of the design that will guide the Part 1 and 2 dose-escalation stages of this study and of its operating characteristics through simulations. All analyses were performed using the crmPack library ([Sabanés Bové et al. 2019](#)) in the R programming environment R version 3.6.1 (2019-07-05) ([R Core Team 2017](#)).

1. Rationale for Model-Based Design

Dose-escalation of this study will use a Bayesian model-based approach, i.e., the mCRM-EWOC design ([Neuenschwander et al. 2008](#)). The use of Bayesian model-based phase I designs has been advocated by Rogatko ([2007](#)) and is one of the key elements of the FDA's Critical Path Initiative. Clinical judgment can always override the Bayesian adaptive design recommendations in the dose-selection process.

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

2. Statistical Model

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

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

where

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

and d^* is the reference dose (in this case $d^* = 1000$ mg).

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

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

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

2.1 General Model Setting

2.1.1 Dose Grid

The following dose grid has been used:

From 5 to 50, by 1; from 55 to 100, by 5; from 110 to 500, by 10; from 550 to 1500, by 25 mg.

2.1.2 Maximum Dose Increments

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

- **Maximum Dose Increments Relative to Dose Levels:**

From 0 mg up to 50 mg, 200% maximum increments are allowed. From 50 mg, 100% maximum increments are allowed.

- **Maximum Dose Increments Relative to DLT:**

Until 1 DLT a maximum increment of 200% is allowed, if 1 DLT the maximum increment becomes 50%, and if 2 or more DLTs a maximum increment of 33% is allowed.

After the two rules have been applied, the maximum allowed dose increment will be defined as the lower increment of the two resulting increments. Note that the EWOC specification includes the maximum dose increment of 200% up to 50 mg as that yields the desired dose-escalation scheme of tripling only up to 150 mg.

2.1.3 Stopping Rules

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

- **Enough information on MTD:**

At least a minimum of 12 participants evaluated and at least 6 participants have been accrued near the MTD dose (where near means differing from the MTD by at most 10%) and the posterior probability that the MTD dose lies within the target toxicity interval is above 50% **OR**

- **Maximum dose is safe:**

At least 6 participants have been observed at the maximum dose or near (differing from the maximum dose by at most 5%) and it is at least 50% likely that the probability of a DLT for the maximum dose is below 0.2. **OR**

- **Maximum number of participants:**

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

2.2 Model Prior

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

This minimally informative prior neutral component will be constructed based on the assumed not toxic and toxic dose levels. It is conservatively assumed that it would be very unlikely (with a 80% confidence) that a 30% or higher DLT rates are associated with the first dose of 16 mg of the dose-escalation of RO7300490 and that it would be very unlikely (with 90% confidence) that a 30% or lower DLT rate are associated with the dose of 1500 mg.

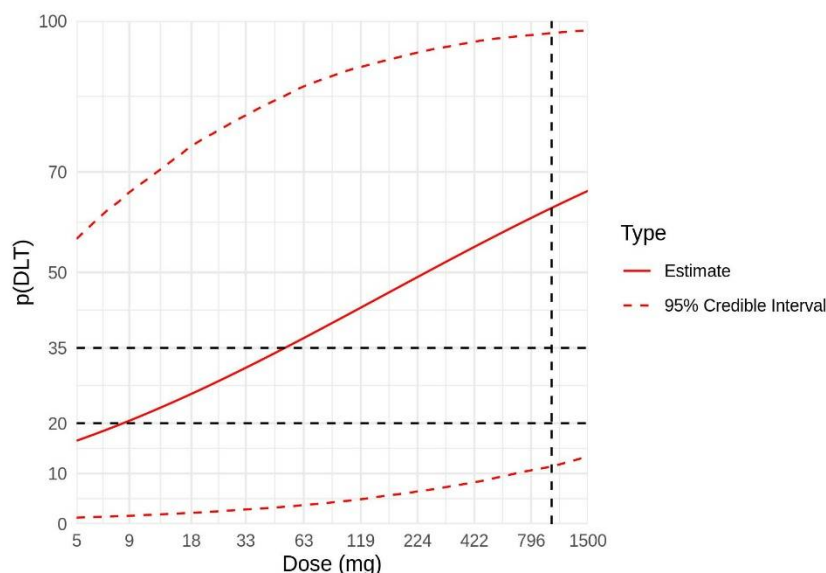
The parameters of the minimally informative prior are listed below (3):

$$\begin{aligned} \mu = (\alpha, \ln\beta) &= (0.71, -0.66) \\ \Sigma = \begin{pmatrix} \sigma_{\alpha}^2 & \sigma_{\alpha \ln\beta} \\ \sigma_{\alpha \ln\beta} & \sigma_{\ln\beta}^2 \end{pmatrix} &= \begin{pmatrix} 2.18 & 0.16 \\ 0.16 & 0.02 \end{pmatrix} \end{aligned} \quad (3)$$

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

The prior distribution used to determine the dose-escalation decision for this study is shown in [Figure 1](#).

Figure 1 Prior Distribution of the DLT-dose response curve in the mCRM-EWOC Design



3. Model Performance Evaluation

To illustrate how the design will perform, different escalation scenarios are explored and results are tabulated in [Table 1](#). Each column represents four different situations: which dose would the model recommend, after seeing no DLTs in previous cohorts and when 1, 2, or 3 DLTs are observed in the current cohort. The evaluation is based on cohort size= 3, 'stop' indicates that the model would stop escalating and the study would be halted. The dose-escalations commence at 16 mg and go up to a maximum of 1500 mg.

As can be seen from the [Table 1](#), in general in presence of no DLTs the model will suggest to escalate close to what the maximum increments allow, while in presence of one DLT, the increments are limited. Then, with 2 or 3 DLTs, the model always recommends to de-escalate or stop. We can overrule the recommendation of the model to escalate if there are 2 DLTs. Therefore, the results show that the design will adequately adapt the dose in the presence of observed DLTs.

Table 1 Dose Escalation Mock Runs

Dose Level	Dose (mg)	Next Dose (% Increment) if No DLT	Next Dose (% Increment) if 1 DLT	Next Dose (% Increment) if 2 DLTs	Next Dose (% Increment) if 3 DLTs
1	16	48 (200%)	13 (-19%)	stop	stop
2	48	140 (192%)	50 (4%)	17 (-65%)	7 (-85%)
3	140	280 (100%)	160 (14%)	60 (-57%)	27 (-81%)
4	280	550 (96%)	410 (46%)	160 (-43%)	75 (-73%)
5	550	1100 (100%)	825 (50%)	390 (-29%)	180 (-67%)
6	1100	1500 (36%)	1500 (36%)	850 (-23%)	410 (-63%)

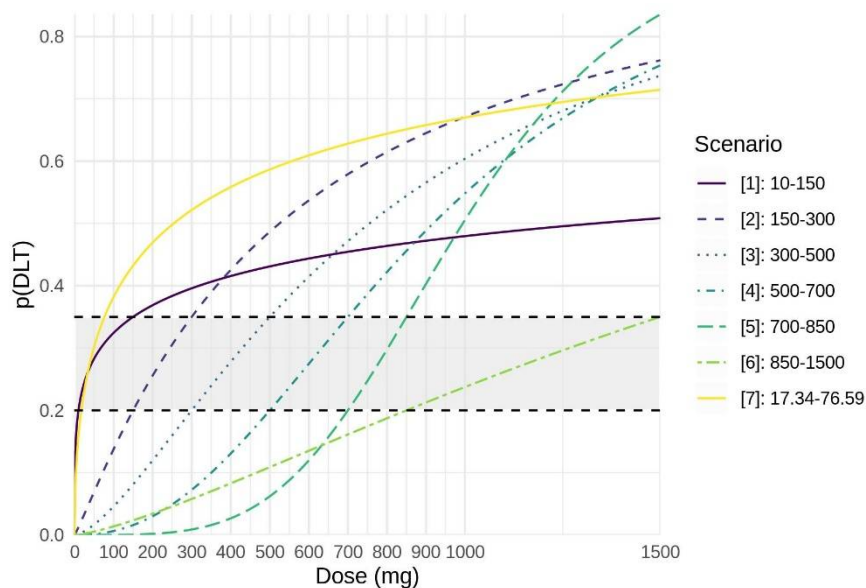
4. Simulation Study

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

4.1 Dose-Toxicity Scenarios

Seven scenarios were explored (see [Figure 2](#)). The first 6 represent dose ranges with decreasing chances of reaching an MTD, while the last one considers the toxicity depicted in the prior as true toxicity. Some scenarios are extreme; however, they remain informative on how the model would eventually perform, despite the extremely low likelihood of the scenario.

Figure 2 True Target DLT-Dose-Response Scenarios Used for Simulations



4.2 Simulation Results

For each of the scenarios, 1000 trials were simulated. The design is evaluated using the following criteria: the MTD chosen, the number of subjects treated at doses higher than the MTD and the total number of subjects treated. For each criterion, the median (with the 10th and 90th percentiles) value from the 1000 simulations is reported in [Table 2](#).

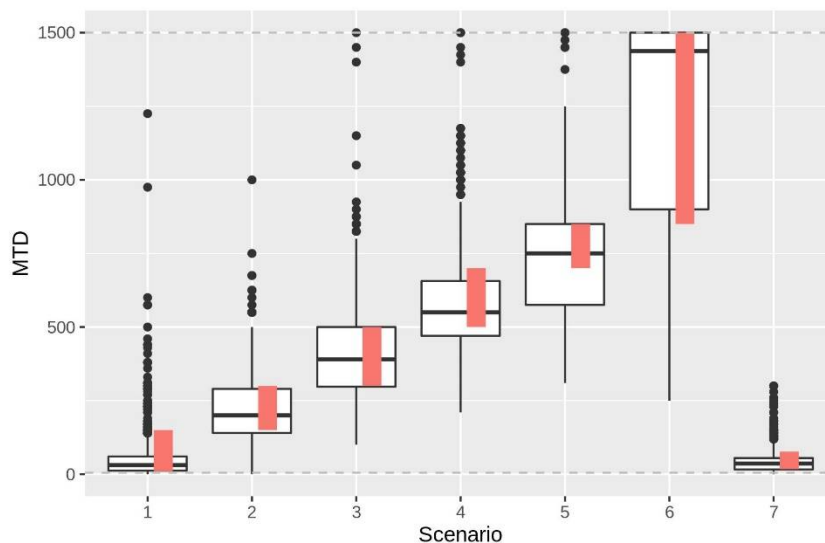
Table 2 Operating Characteristics of the mCRM-EWOC Design for Part 1 with Respect to the Chosen Scenarios Based on 1000 Simulations for Each Case.

Scenario	True Target Dose Range	Overall N of Participants	N Participants Treated above Target Toxicity	Proportion of DLTs in the Trials	Dose Selected as MTD
1	10-150	24 (3, 39)	0 (0, 6)	26.7% (20%, 66.7%)	31 (0, 130)
2	150-300	30 (21, 45)	3 (0, 15)	21.2% (17.9%, 25.9%)	200 (120, 370)
3	300-500	33 (24, 42)	6 (0, 15)	20% (16.7%, 24.2%)	390 (230, 600)
4	500-700	33 (27, 42)	6 (0, 15)	20% (16.7%, 23.1%)	550 (399, 825)
5	700-850	33 (27, 42)	6 (3, 12)	18.8% (16.7%, 22.2%)	750 (550, 1025)
6	850-1500	30 (24, 42)	0 (0, 0)	14.3% (6.7%, 20%)	1437.5 (625, 1500)
7	17.34-76.59	24 (6, 36)	0 (0, 15)	26.7% (20.8%, 50%)	36 (0, 90.5)

From these simulations, it can be seen that the design is able to provide a reliable estimate of the MTD: the median of the doses selected as MTD is always within the target toxicity dose range.

This is also shown in [Figure 3](#), where the distribution of MTDs identified in the various simulation runs is plotted against the true target toxicity range (red bars) for each scenario.

Figure 3 Summary of 1000 Simulations: Plot of Distribution of MTDs versus Target Toxicity Range



In addition, the number of participants treated over the dose-toxicity interval is quite limited.

The performance of the algorithm also is further confirmed by the median number of DLTs observed in the simulations, which is always under 22%, with the exception of

scenario 1, where it is 26.7%. Lastly, the estimated sample size required to give an MTD recommendation in all scenarios seems to be reasonable, with a median of 33 participants.

References

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Appendix 7

Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immunotherapy-specific response criteria adaptations to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; [Eisenhauer et al. 2009](#)) have been developed to allow for unconventional response and progression patterns. These include modified RECIST v1.1 for immune-based therapeutics (iRECIST; [Seymour et al. 2017](#)), which was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials.

Response evaluation through use of iRECIST requires collection of tumor assessment data after radiographic progression per RECIST v1.1. Details regarding lesion evaluation are described below. When not otherwise specified, RECIST v1.1 conventions will apply. Criteria for determining overall response at a single 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). It will instead be derived manually and retrospectively 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 (e.g., non-lymph node lesions must be ≥ 10 mm on the longest diameter; new lymph nodes must be ≥ 15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment time points (see [Table 1](#)).

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 ≥ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is < 10 mm, the lymph node should not be considered pathological and

should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent 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	<ul style="list-style-type: none"> Measurements should be continued according to RECIST v1.1 conventions.
Non-target lesions	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 TIMEPOINT

Time point response per iRECIST will be derived manually and retrospectively by the Sponsor. For a complete description of the iRECIST criteria, see [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 Canc*. 2009;45:228–47.
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Appendix 8

New Response Evaluation Criteria in Solid Tumors Version 1.1

Modified Excerpt from Original Publication with Addition of Supplementary Explanations

1. MEASURABILITY OF TUMOR AT BASELINE

1.1 DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions, which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also Section [2.2](#) on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical exam that 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, positron emission tomography (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) because they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases, can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with previous local treatment:

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

1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

1.2.1 Measurement of Lesions

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

1.2.2 Method of Assessment

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

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

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

2. TUMOR RESPONSE EVALUATION

2.1. ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed in Section [1.1.1](#)).

2.2. BASELINE DOCUMENTATION OF ‘TARGET’ AND ‘NON-TARGET’ LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Paired organs (e.g. kidneys) and the entire lymphatic system are considered one organ.

This means in instances where participants have only one or 2 organ sites involved a maximum of 2 (one site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is ≥ 10 mm by CT scan).

Target lesions should be selected 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 because they are normal anatomical structures, which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1, pathological 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 \times 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions.

Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (see also Section 2.3.4).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. RESPONSE CRITERIA

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1. Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

Target lesions that become 'too small to measure': while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure

and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form:

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

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign <).

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

Progressive Disease: Unequivocal progression (see Section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4. Special Notes on Assessment of Progression of Non-target Disease

When the participant also has measurable disease: in this setting, to achieve 'unequivocal progression' 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 progressive disease 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 progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.3.5. New Lesions

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

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

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

2.4 EVALUATION OF RESPONSE

2.4.1 Time-Point Response (Overall Response)

It is assumed that at each protocol specified time point, a response assessment occurs. A summary of the overall response status calculation at each time point for participants who have measurable disease at baseline is provided in [Table 1](#).

When participants have non-measurable (therefore non-target) disease only, [Table 2](#) is to be used.

Table 1 Time-Point Response – Target (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, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.			

Abbreviations: w/wo = with or without.

Table 2 Time-Point Response – Non-Target Lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD ^a
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease, and NE = inevaluable. a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

2.4.2 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the participant is not evaluable at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of progressive disease.

For example, if a participant had a baseline sum of 50 mm with 3 measured lesions and during study only 2 lesions were assessed, but those gave a sum of 80 mm, the participant will have achieved progressive disease status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be “Unable to Assess” because the participant is not evaluable. Similarly, if one or more non-target lesions are indicated as ‘not assessed’, the response for non-target lesions should be “Unable to Assess” (except where there is clear progression). Overall, response would be “Unable to Assess” if either the target response or the non-target response is “Unable to Assess” (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point ([Table 3](#)).

Table 3 Best Overall Response when Confirmation is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR ^a
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the case report form (CRF).

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such participants is to be determined by evaluation of target and non-target disease as shown in [Table 1](#), [Table 2](#), and [Table 3](#).

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

Reference:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Canc. 2009;45(2):228-47.

Appendix 9 ASTCT Cytokine Release Syndrome Consensus Grading

CRS Grade ^a	Clinical Parameter:				
	Fever ^b		Hypotension		Hypoxia
Grade 1	Temperature $\geq 38^{\circ}\text{C}$	with	None	and/ or ^c	None
Grade 2	Temperature $\geq 38^{\circ}\text{C}$		Not requiring vasopressors		Requiring low-flow nasal cannula ^d or blow-by
Grade 3	Temperature $\geq 38^{\circ}\text{C}$		Requiring a vasopressor with or without vasopressin		Requiring high-flow nasal cannula, facemask, nonrebreather mask or Venturi mask
Grade 4	Temperature $\geq 38^{\circ}\text{C}$		Requiring multiple vasopressors (excluding vasopressin)		Requiring positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT = American Society for Transplantation and Cellular Therapy, BiPAP = Bilevel positive airway pressure, CPAP = continuous positive airway pressure, CRS = Cytokine Release Syndrome; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

^a CRS grading per ASTCT (Lee 2019). The organ toxicities associated with CRS should be graded according to NCI CTCAE v5.0.

^b Fever is defined as temperature $\geq 38^{\circ}\text{C}$, not attributable to any other cause. In participants who develop CRS, and then receive antipyretic or anticytokine therapy (e.g. tocilizumab or steroids), fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

^c CRS grade is determined by the more severe event: hypotension or hypoxia, not attributable to any other cause.

^d Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Reference:

Lee DW, Santomaso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transpl. 2019;25(4):625-38.

Appendix 10

Management Guidelines for Immune-Mediated Adverse Events Associated with RO7300490 and/or Combination Therapy with RO7300490 and Atezolizumab

Atezolizumab will be administered at doses of 840 mg Q2W or, if justified by emerging safety, PK, PD, and efficacy data, 1200 mg Q3W (see Section 4.1). There will be no other dose modifications for atezolizumab in this study. Atezolizumab will not be administered without co-administration of RO7300490 in this study. Specific guidance on interruptions in the administration of RO7300490 and/or atezolizumab are presented in Section 6.6 and this Appendix.

Although immune-mediated toxicities associated with RO7300490 have not been fully identified, those associated with, or possibly associated with atezolizumab treatment should be managed according to standard medical practice, independent of their specific association with RO7300490 or with atezolizumab. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of RO7300490 (Part 1) or RO7300490 in combination with atezolizumab (Part 2) may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The Investigator should consider the benefit–risk balance a given participant may be experiencing prior to further administration of RO7300490 alone or in combination with atezolizumab. In participants who have met the criteria for permanent discontinuation, resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered if the participant is deriving benefit and has fully recovered from the immune-mediated event. Please refer to Section 6.6 for further information.

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab, although association of these findings with RO7300490 is unknown. Participants will be assessed for pulmonary signs and symptoms throughout the study and have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary

embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in [Table 1](#).

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	<ul style="list-style-type: none"> Continue RO7300490 and/or atezolizumab and monitor closely. Re-evaluate on serial imaging. Consider participant referral to pulmonary specialist. <i>For Grade 1 pneumonitis, consider withholding RO7300490 and/or atezolizumab.</i>
Pulmonary event, Grade 2	<ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset.^a Refer participant to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab.^b If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	<ul style="list-style-type: none"> Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c Bronchoscopy or BAL is recommended. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = Bronchoscopic alveolar lavage.

^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.

^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab, although association of this finding with RO7300490 is unknown. Eligible participants must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in [Table 2](#).

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
<i>Guidelines for patients <u>without</u> hepatocellular carcinoma</i>	
Hepatic event, Grade 1	<ul style="list-style-type: none">Continue RO7300490 and/or atezolizumab.Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	<p>All events:</p> <ul style="list-style-type: none">Monitor LFTs more frequently until return to baseline values. <p>Events of > 5 days' duration:</p> <ul style="list-style-type: none">Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset. ^aInitiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab. ^bIf event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c
Hepatic event, Grades 3 or 4	<ul style="list-style-type: none">Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^cConsider participant referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Guidelines for patients <u>with</u> hepatocellular carcinoma	
<p>AST/ALT is within normal limits at baseline and increases to $>3 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$</p> <p>or</p> <p>AST/ALT is $> \text{ULN}$ to $\leq 3 \times \text{ULN}$ at baseline and increases to $>5 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$</p> <p>or</p> <p>AST/ALT is $>3 \times \text{ULN}$ to $\leq 5 \times \text{ULN}$ at baseline and increases to $>8 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$</p>	<ul style="list-style-type: none"> • Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset. ^a • Monitor LFTs more frequently until return to baseline values. • For events of >5 days' duration, consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume RO7300490 and/or atezolizumab. ^b • If event does not resolve to baseline or to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c
<p>AST or ALT increases to $>10 \times \text{ULN}$ or total bilirubin increases to $>3 \times \text{ULN}$</p>	<ul style="list-style-type: none"> • Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over ≥ 1 month.

LFT=Liver function test.

^a Any temporary treatment interruption beyond 2 cycles to allow corticosteroids taper to prednisone dose (or dose equivalent) $\leq 10\text{mg/day}$ must be discussed -with the Medical Monitor. RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to the equivalent of $\leq 10 \text{ mg/day}$ oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of $\leq 10 \text{ mg/day}$ oral prednisone before RO7300490 and/or atezolizumab can be resumed.

^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab, although association of this finding with RO7300490 is unknown. Management guidelines for diarrhea or colitis are provided in [Table 3](#).

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

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

Event	Management
Diarrhea or colitis, Grade 1	<ul style="list-style-type: none"> • Continue RO7300490 and/or atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	<ul style="list-style-type: none"> • Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset. ^a • Initiate symptomatic treatment. • Referral of participant to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c
Diarrhea or colitis, Grade 3	<ul style="list-style-type: none"> • Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset. ^a • Refer participant to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c
Diarrhea or colitis, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c • Refer participant to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = Gastrointestinal.

- ^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.
- ^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab, although association of these findings with RO7300490 is unknown. Management guidelines for endocrine events are provided in [Table 4](#).

Participants with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The participant should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotrophic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	<ul style="list-style-type: none"> Continue RO7300490 and/or atezolizumab. Initiate treatment with thyroid replacement hormone. Monitor TSH <i>closely</i>.
Symptomatic hypothyroidism	<ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab. Initiate treatment with thyroid replacement hormone. Monitor TSH <i>closely</i>. Consider participant referral to endocrinologist. Resume RO7300490 and/or atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	<p>TSH ≥ 0.1 mU/L and < 0.5 mU/L:</p> <ul style="list-style-type: none"> Continue RO7300490 and/or atezolizumab. Monitor TSH every 4 weeks. <i>Consider patient referral to endocrinologist.</i> <p>TSH < 0.1 mU/L:</p> <ul style="list-style-type: none"> Follow guidelines for symptomatic hyperthyroidism. <i>Consider patient referral to endocrinologist.</i>
Symptomatic hyperthyroidism	<ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab. Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider participant referral to endocrinologist. Resume RO7300490 and/or atezolizumab when symptoms are controlled and thyroid function is improving. Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. ^c
Symptomatic adrenal insufficiency, Grade 2–4	<ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset. ^a Refer participant to endocrinologist. Perform appropriate imaging. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better and participant is stable on replacement therapy, resume RO7300490 and/or atezolizumab. ^b If event does not resolve to Grade 1 or better or participant is not stable on replacement therapy while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c
Hyperglycemia, Grade 1 or 2	<ul style="list-style-type: none"> Continue RO7300490 and/or atezolizumab. Investigate for diabetes. If participant has Type 1 diabetes, treat as a Grade 3 event. If the participant does not have Type 1 diabetes, treat as per institutional guidelines. Monitor for glucose control.

Event	Management
Hyperglycemia, Grade 3 or 4	<ul style="list-style-type: none"> • Withhold RO7300490 and atezolizumab. • Initiate treatment with insulin. • <i>Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.</i> • Monitor for glucose control. • Resume RO7300490 and/or atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	<ul style="list-style-type: none"> • Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset. ^a • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab. ^b • If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	<ul style="list-style-type: none"> • Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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

^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.

^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	<ul style="list-style-type: none">• Continue RO7300490 and/or atezolizumab.• Participant referral to ophthalmologist is strongly recommended.• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.• If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	<ul style="list-style-type: none">• Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset.^a• Participant referral to ophthalmologist is strongly recommended.• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.• If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab.^b• If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c
Ocular event, Grade 3 or 4	<ul style="list-style-type: none">• Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c• Refer participant to ophthalmologist.• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.

^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab, although association of this finding with RO7300490 is unknown. Immune-mediated myocarditis should be suspected in any participant presenting with signs or symptoms suggestive of myocarditis (including, but not limited to), laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.*

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a participant who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

Participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 6](#).

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grades 2- 4	<ul style="list-style-type: none">• Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^a• Refer participant to cardiologist.• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO=Extracorporeal membrane oxygenation; VAD=Ventricular assist device.

^a Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

RO7300490 must be administered after atezolizumab (Part 2 and 3 only). Therefore, this section is applicable to infusion-related reaction (IRR) or cytokine release syndrome (CRS) associated with atezolizumab only.

No pre-medication is indicated for the administration of Cycle 1 of atezolizumab. However, participants who experience an IRR or CRS with atezolizumab may receive pre-medication with antihistamines, anti-pyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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

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

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome associated with atezolizumab only

Event	Management
<u>Grade 1</u> ^a Fever ^b with or without constitutional symptoms	<ul style="list-style-type: none"> • Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,^c including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in participants with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral pre-medication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
<u>Grade 2</u> ^a Fever ^b with hypotension not requiring vasopressors <u>and/or</u> Hypoxia requiring low-flow oxygen ^d by nasal cannula or blow-by	<ul style="list-style-type: none"> • Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment.^c • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.^e • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize participant (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral pre-medication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
<u>Grade 3</u> ^a	<ul style="list-style-type: none"> • Permanently discontinue atezolizumab and contact Medical Monitor.^f • Administer symptomatic treatment.^c

Event	Management
Fever ^b with hypotension requiring a vasopressor (with or without vasopressin) <u>and/or</u> Hypoxia requiring high-flow oxygen ^d by nasal cannula, face mask, non-rebreather mask, or Venturi mask	<ul style="list-style-type: none"> For hypotension, administer IV fluid bolus and vasopressor as needed. Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy.^e Hospitalize participant until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit participant to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for participants who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
<u>Grade 4^a</u> Fever ^b with hypotension requiring multiple vasopressors (excluding vasopressin) <u>and/or</u> Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	<ul style="list-style-type: none"> Permanently discontinue atezolizumab and contact Medical Monitor.^f Administer symptomatic treatment.^c Admit participant to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy.^e For participants who are refractory to anti-cytokine therapy, experimental treatments^g may be considered at the discretion of the investigator and in consultation with the Medical Monitor. Hospitalize participant until complete resolution of symptoms.

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

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

- ^a Grading system for management guidelines is based on ASTCT consensus grading for CRS. *The ASTCT Cytokine Release Syndrome Consensus Grading will also be used when reporting CRS*; NCI CTCAE v 5.0 should be used when reporting severity of IRRs, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
- ^b Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In participants who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
- ^c Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
- ^d Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
- ^e There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors ([Rotz et al. 2017](#); [Adashek and Feldman 2019](#)), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
- ^f Resumption of atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the event. *The decision to re-challenge patients with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.* For subsequent infusions, administer oral pre-medication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Pre-medication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit–risk ratio.
- ^g For information on experimental treatments for CRS, refer to [Riegler et al. 2019](#).

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab, although association of these findings with RO7300490 is unknown. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in [Table 8](#).

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	<p>Amylase and/or lipase > 1.5–2.0 × ULN:</p> <ul style="list-style-type: none"> Continue RO7300490 and/or atezolizumab. Monitor amylase and lipase weekly. For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. <p>Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:</p> <ul style="list-style-type: none"> Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	<ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset.^a Refer participant to GI specialist. Monitor amylase and lipase every other day. If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab.^b If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c For recurrent events, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c
Immune-mediated pancreatitis, Grade 2 or 3	<ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset.^a Refer participant to GI specialist. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab.^b If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c For recurrent events, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c
Immune-mediated pancreatitis, Grade 4	<ul style="list-style-type: none"> Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c Refer participant to GI specialist. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

Event	Management
	<ul style="list-style-type: none"> If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = Gastrointestinal.

- ^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.
- ^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. An association of these findings with RO7300490 is unknown. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in [Table 9](#).

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	<ul style="list-style-type: none"> Continue RO7300490 and/or atezolizumab. Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	<ul style="list-style-type: none"> Continue RO7300490 and/or atezolizumab. Consider participant referral to dermatologist for evaluation and, if indicated, biopsy. Initiate treatment with topical corticosteroids. Consider treatment with higher-potency topical corticosteroids if event does not improve. <i>If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.</i>

Event	Management
Dermatologic event, Grade 3	<ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset.^a Refer participant to dermatologist for evaluation and, if indicated, biopsy. Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab.^b If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c
Dermatologic event, Grade 4	<ul style="list-style-type: none"> Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	<p>Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:</p> <ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. Follow the applicable treatment and management guidelines above. If Stevens-Johnson syndrome or toxic epidermal necrolysis <i>is confirmed</i>, permanently discontinue RO7300490 and atezolizumab.

^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.

^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single agent atezolizumab, although association of these findings with RO7300490 is unknown. Participants may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between

alternative etiologies. Management guidelines for neurologic disorders are provided in [Table 10](#).

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	<ul style="list-style-type: none"> Continue RO7300490 and/or atezolizumab. Investigate etiology.
Immune-mediated neuropathy, Grade 2	<ul style="list-style-type: none"> Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset.^a Investigate etiology <i>and refer patient to neurologist</i>. Initiate treatment as per institutional guidelines. If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab.^b If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c
Immune-mediated neuropathy, Grade 3 or 4	<ul style="list-style-type: none"> Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c <i>Refer patient to neurologist</i>. Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	<ul style="list-style-type: none"> Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c Refer participant to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.

^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab, although association of this finding with RO7300490 is unknown. Immune-mediated meningoencephalitis should be suspected in any participant presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

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

Participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 11](#).

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	<ul style="list-style-type: none">• Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^a• Refer participant to neurologist.• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab, although association of this finding with RO7300490 is unknown. Eligible participants must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Participants with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Participants with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 12](#).

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	<ul style="list-style-type: none">• Continue RO7300490 and/or atezolizumab.• Monitor kidney function, including creatinine <i>and urine protein</i>, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	<ul style="list-style-type: none">• Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset. ^a• Refer participant to renal specialist.• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.• If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab. ^b• If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. ^c
Renal event, Grade 3 or 4	<ul style="list-style-type: none">• Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.• Refer participant to renal specialist and consider renal biopsy.• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

- ^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*
- ^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.
- ^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab, although association of this finding with RO7300490 is unknown. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.*

Participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table 13](#).

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	<ul style="list-style-type: none">• Continue RO7300490 and/or atezolizumab.• Refer participant to rheumatologist or neurologist.• Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	<ul style="list-style-type: none">• Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset^a and contact Medical Monitor.• Refer participant to rheumatologist or neurologist.• Initiate treatment as per institutional guidelines.• Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.• If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab.^b• If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c
Immune-mediated myositis, Grade 3	<ul style="list-style-type: none">• Withhold RO7300490 and atezolizumab for up to 12 weeks after event onset^a and contact Medical Monitor.• Refer participant to rheumatologist or neurologist.• Initiate treatment as per institutional guidelines.• Respiratory support may be required in more severe cases.• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.• If event resolves to Grade 1 or better, resume RO7300490 and/or atezolizumab.^b• If event does not resolve to Grade 1 or better while withholding RO7300490 and atezolizumab, permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c• For recurrent events, treat as a Grade 4 event.

Event	Management
Immune-mediated myositis, Grade 4	<ul style="list-style-type: none"> • Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor.^c • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if the participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

^a RO7300490 and atezolizumab may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the Investigator and in alignment with the protocol requirements for the duration of treatment and documented. The Medical Monitor is available to advise as needed.*

^b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7300490 and/or atezolizumab can be resumed.

^c Resumption of RO7300490 as a single agent or in combination with atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with RO7300490 alone or in combination with atezolizumab should be based on Investigator's assessment of benefit-risk and documented. The Medical Monitor is available to advise as needed.*

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

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

- Fever ≥ 38.5°C
- Splenomegaly

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

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

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

Participants with suspected HLH or MAS should be treated according to the guidelines in [Table 14](#).

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

Event	Management
Suspected HLH or MAS	<ul style="list-style-type: none"> • Permanently discontinue RO7300490 and atezolizumab and contact Medical Monitor. • Consider participant referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH=hemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome.

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Appendix 11

Schedule of Assessments in Case of Tocilizumab Administration for Cytokine-Release Syndrome

	Pre-TCZ	TCZ	Post-TCZ						
Time window relative to TCZ dosing	within 24 h		+15 min post EOI	6h (± 3h) post-EOI ^a	1 day (24h ± 4h) post-EOI	2 days (48h ± 4h) post-EOI ^a	3 days (72h ± 4h) post-EOI ^a	8 days (192h ± 48h) post-EOI ^a	EoT
TCZ administration (8 mg/kg for patients ≥ 30kg; 12 mg/kg for patients < 30kg; dose exceeding 800mg per infusion not recommended)		x							
Vital Signs (respiratory rate, heart rate, systolic and diastolic blood pressure [in a seated or supine position], temperature, and oxygen)			At least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization						
Vasopressor (document the type and dose in the concomitant medication eCRF)	x		Record at least every 6 hours until vasopressor are discontinued						
FiO ₂	x		Record at least every 6 hours until patient on room air						
Local Laboratory Assessments									
Hematology (leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, and differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells])	x			x	x	x	x	x	
Blood Chemistry (sodium, potassium, chloride, bicarbonate, glucose, albumin, total protein, blood urea nitrogen, creatinine, creatinine clearance [by Cockcroft-Gault formula], calcium, magnesium, phosphorous, uric acid, ALP, ALT, AST, bilirubin, LDH, GGT, CRP and ferritin)	x			x	x	x	x	x	
Coagulation (INR, aPTT[or PTT], PT and fibrinogen)	x			x	x	x	x	x	
Infection workup (for bacterial, fungal and viral infections as clinically indicated)	x								
Central Laboratory Assessments									
Serum IL-6 pharmacodynamic markers (include IL-6, sIL-6R) ^b	x		x ^c	x	x	x	x	x	
Serum PK TCZ ^b	x		x ^c	x	x	x	x	x	x
Serum ADA TCZ ^d	x								x

ADA = Anti-drug antibody; EOI = End of TCZ infusion; EoT = End of treatment visit (8 weeks after the last administration of TCZ); eCRF = Electronic Case Report Form; TCZ = Tocilizumab.

^a After first administration of TCZ only.

^b The samples should be taken as soon as possible, i.e., ideally at the time of the development of cytokine release syndrome or, if not feasible, at the earliest possible convenience. If sampling timepoints fall during overnight hours and staff is not available for collecting/processing samples, collection can be delayed until the following morning. Every attempt should be made to collect the samples at the earliest possible convenience. If sample collection is delayed until the following morning, it is critical that the actual sampling collection time and date be documented in the eCRF.

^c Samples will be drawn from the arm not used for TCZ administration.