Official Title:	A First-in-Human, Open-Label, Multicenter, Dose-Escalation Phase I Clinical Study of Single-Agent RO7172508 in Patients With Locally Advanced and/or Metastatic CEA-Positive Solid Tumors
NCT Number:	NCT03539484
Document Dates:	Protocol Version 4: 26-December-2018

PROTOCOL

TITLE:	**A FIRST-IN-HUMAN, OPEN-LABEL, MULTICENTER, DOSE-ESCALATION PHASE I CLINICAL STUDY OF SINGLE-AGENT RO7172508 IN PATIENTS WITH LOCALLY ADVANCED AND/OR METASTATIC CEA-POSITIVE SOLID TUMORS**
PROTOCOL NUMBER:	BP40092
VERSION:	*4*
EUDRACT NUMBER:	2017-003834-10
IND NUMBER:	140737
TEST PRODUCT:	RO7172508 *and obinutuzumab*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 18 Dec 2017
DATE AMENDED:	Version 2: 20 Apr 2018 Version 3: *6 Nov 2018* ***Version 4:*** *See electronic date stamp below*

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	26-Dec-2018 12:08:00

PROTOCOL ACCEPTANCE FORM

TITLE:	**A FIRST-IN-HUMAN, OPEN-LABEL, MULTICENTER, DOSE-ESCALATION PHASE I CLINICAL STUDY OF SINGLE-AGENT RO7172508 IN PATIENTS WITH LOCALLY ADVANCED AND/OR METASTATIC CEA-POSITIVE SOLID TUMORS**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Since the changes made under Protocol BP40092 version 3 and Protocol BP40092 version 4 followed each other in quick succession and Protocol BP40092 version 3 was not submitted to any ethics committees or regulatory authorities, the rationale of Protocol BP40092 version 3 has been kept and aggregated with the rationale of Protocol BP40092 version 4. Therefore, the changes made throughout this protocol reflect those changes made under both Protocol BP40092 version 3 and version 4.

Protocol BP40092 version 3 and Protocol BP40092 version 4 have been amended for the following reasons:

Major Changes

1. Addition of obinutuzumab pretreatment

Rationale: Previous studies with T-cell bispecifics against CEA (cibisatamab [RO6958688, CEA-TCB]) have shown that significant proportions of patients may develop anti-drug antibodies (ADAs). ADA formation can lead to loss of exposure, in addition to potential safety events by unintended activation of peripheral T-cells via CD3 crosslinking through ADA-TCB complexes.

B-cell depletion by obinutuzumab (anti-CD20) pretreatment has recently been introduced as a way to mitigate these effects. While the ADA risk with RO7172508 is not known at this time, language describing an algorithm to evaluate obinutuzumab pretreatment was added to the protocol to prepare for an eventuality of ADA formation observed in study BP40092.

Sections: 2.1 Study Rationale, 2.2.2 Background, 2.3 Benefit/Risk Assessment, 4.1.3 Obinutuzumab Pre-treatment, 4.3.2 Obinutuzumab, 5.2 Exclusion Criteria, 6.0 Treatments, 6.1.1 Premedications, and Appendix 8.

2. Evaluation of exploratory endpoints according to modified RECIST (mRECIST) was removed

With protocol version 4, the Sponsor specific evaluation of the exploratory endpoints progression-free survival, PFS, objective response, duration of response (DOR), and disease control rate (DCR) according to modified RECIST was removed from the exploratory study objectives. These endpoints will continue to be evaluated according to industry standards of RECIST 1.1 (secondary endpoints) and immune modified RECIST (iRECIST) (exploratory endpoints).

Sections: 3 Objectives and Endpoints, 8.1.1 Tumor and Response Evaluations, 9.4.2 Efficacy Analyses, Appendix 6 New Response Evaluation Criteria in Solid Tumors [RECIST] – Version 1.1 – Modified Excerpt from Original Publication with Addition of Supplementary Explanations (updated), Appendix 7 Modified RECIST v1.1 for Immune-based Therapeutics (iRECIST) (added).

3. Option to administer subcutaneous cohorts Q3W

Rationale: Subcutaneous administration of RO7172508 QW had been planned in the previous protocol versions, once the IV dose escalation reached 6 mg to evaluate this route of administration. In the current amendment, an additional option was added to evaluate RO7172508 SC Q3W starting from a dose of 2 mg. This allows evaluation of SC RO7172508 route of administration in the event the MTD/OBD of IV RO7172508 is between 2 and 6 mg, which would not allow the planned QW dosing starting at 2 mg (minimal injectable dose).

Sections: 4.1 Overall Design and 4.1.2.2 Part II: Multiple-Ascending Dose-Escalation.

4. Expansion of sCEA thresholds for doses less than 12 mg as additional inclusion criterion for Part II

Rationale: Preliminary data from the first participants treated in Part I of this study suggest that RO7172508 may bind to circulating soluble CEA (sCEA) impacting exposure and therefore the pharmacodynamic effects of RO7172508. In Part II of the study, selection of participants by sCEA was originally not foreseen (in contrast to Part I). To reduce variability and the impact of sCEA on PK and PD, thresholds of sCEA have been set to limit baseline sCEA levels in participants receiving up to 12 mg of RO7172508. Furthermore, according to protocol version 4, in order to assess the relationship between sCEA and RO7172508 clearance relative to safety, at least 3 participants with low levels of sCEA (≤ 20 ng/mL) will be enrolled in each cohort in Part II to assess the exposure-toxicity relationship. Depending on emerging PK and safety data, the dose escalation may be evaluated taking into account sCEA levels at baseline in a sensitivity analysis (i.e. dose escalating more conservatively in the event toxicity is associated with low baseline sCEA levels).

Sections: 4.2.2 Rationale for Study Population and 5.1 Inclusion Criteria.

5. Updated pre-medication

Rationale: In order to mitigate RO7172508-related toxicity, the use of pre-medication of corticosteroid on Cycle 1 of RO7172508 infusion for IRR/CRS occurrence was updated in protocol version 4 to also mitigate gastrointestinal RO7172508-related toxicity. The dose and timing of corticosteroid use relative to RO7172508 infusion was also updated.

It was added that additional pre-medication regimens may be implemented after agreement between Sponsor and Investigators; these are 5-HT3-receptor antagonist administration and Budesonide. 10 mg metoclopramide (or equivalent anti-emetic) was removed.

Further options regarding the use and timing of pre-medication in subsequent RO7172508 infusions were provided, to enable participants to receive oral corticosteroids from Cycle 2 onwards, as deemed necessary by the Sponsor and/or Investigator.

Sections: 6.1.1 Pre-medication.

6. Updated safety assessments

Rationale: Safety management guidelines for RO7172508 have been updated and aligned with guidelines of in class agent cibisatamab that reflect the evolving evidence and recent discussions with the FDA and EU health authorities.

Sections: 8.2 Safety Assessments, 8.3.8.1 Infusion-Related Reactions/Cytokine-Release Syndrome, and 8.3.8.2 Suspected Tumor Inflammation.

7. Inclusion Criteria 5 – Patients with Colorectal Cancer (CRC)

Inclusion criterion requires central assessment of CEA prior to enrollment, however for CRC participants only, the CEA assessment will be performed but the results are not required to enroll patients.

This change is based on internal prevalence analysis described in the RO7172508 Investigator's Brochure, showing 94% of CRC participants have CEA tumor expression meeting the eligibility criteria, therefore in order to simplify the enrollment process this assessment will be done at baseline retrospectively.

8. Exclusion Criteria 12 – Presence of bilateral lung lesions

Clarification for participants with bilateral lung lesions has been provided. Only unequivocal lesions of >1 cm are to be counted for this criterion, unless there is miliary metastasis-type diffuse disease, then these participants are ineligible.

Minor Changes

Minor changes to the protocol were made to align with the substantial changes specified above and improve consistency and clarity throughout the protocol.

Substantial new information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION *4*
SUMMARY OF CHANGES

The Summary of Changes to this protocol has been added in Appendix 9.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
bpm	Beats per minute
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CD3	Cluster of differentiation 3
CD3ε	CD3 epsilon chain
CEA	Carcinoembryonic antigen
CEACAM5	Carcinoembryonic antigen–related cell adhesion molecule 5
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
CNS	Central nervous system
CR	Complete response
CRC	*Colorectal cancer*
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-Lymphocyte Associated Protein 4
DCR	Disease control rate
DLT	Dose-limiting toxicities
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
eCOA	Electronic clinical outcome assessment

Abbreviation	Definition
EOI	End of infusion
ESF	Eligibility Screening Form
EU	European Union
FDA	Food and Drug Administration
FFPE	Formaldehyde fixed-paraffin-embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA-DR	Human Leukocyte Antigen – antigen D Related
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICOS	Inducible co-stimulator
IEC	Independent Ethics Committee
IFN	Interferon
IgE	Immunoglobulin E
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
iRECIST	Immune modified RECIST
irRC	Immune-related response criteria
IRR	Infusion related reaction
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LDH	Lactate dehydrogenase
LOE	*Loss of exposure*

Abbreviation	Definition
LPLV	Last participant, last visit
MABEL	Minimal anticipated biological effect level
mCRM-EWOC	Modified continual reassessment method with overdose control
MedDRA	Medical Dictionary for Regulatory Activities
MIP	Macrophage Inflammatory Protein
MoA	Mode-of-action
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NGS	Next generation sequencing
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OBD	Optimal biological dose
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
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
PO	Oral
PR	Partial response
PS	Performance status
PT	Prothrombin time
Q3W	Every 3 weeks
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate using the Bazett's correction factor
QTcF	QT corrected for heart rate using the Fridericia's correction factor

Abbreviation	Definition
QW	Once a week
RBC	Red blood cell
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RR	Rate of response
SAE	Serious adverse event
SC	Subcutaneous
sCD25	Soluble CD25
sCEA	Serum CEA
SD	Stable disease
SI	International System of Units
SoA	Schedule of activities
SLD	Sum of longest diameters
SOC	Standard of care
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
$T_{1/2}$	Half-life
TCB	T-cell bispecific
TCR	T-cell receptor
TCZ	*Tocilizumab*
TID	3 times a day
TIL	Tumor infiltrating lymphocytes
TIM3	T-cell immunoglobulin and mucin domain 3
T_{max}	Time of maximum concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States
V	Volume of distribution
Vss	Volume of distribution at steady state
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:	**A FIRST-IN-HUMAN, OPEN-LABEL, MULTICENTER, DOSE-ESCALATION PHASE I CLINICAL STUDY OF SINGLE-AGENT RO7172508 IN PATIENTS WITH LOCALLY ADVANCED AND/OR METASTATIC CEA-POSITIVE SOLID TUMORS**
SHORT TITLE	**Phase 1 Study of RO7172508 in Patients with CEA-Positive Solid Tumors**
PROTOCOL NUMBER:	BP40092
VERSION:	*4*
TEST PRODUCT:	RO7172508 *and obinutuzumab*
PHASE:	I

RATIONALE

RO7172508 is a T-cell bispecific (TCB) antibody targeting carcinoembryonic antigen (CEA) expressed on tumor cells and cluster of differentiation 3 (CD3) epsilon chain (CD3ε) present on T-cells. RO7172508 has shown an increased affinity to CEA, higher potency, and prolonged half-life compared with RO6958688 *(cibisatamab)*, a TCB targeting CEA under clinical development, which has induced objective radiological responses as a single agent and in combination with a programmed death-ligand 1 (PD-L1) checkpoint inhibitor (atezolizumab).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the maximum-tolerated dose (MTD) and/or the optimal biological dose (OBD) for intravenous (IV) and subcutaneous (SC) administrations of RO7172508 as monotherapy *and with obinutuzumab pretreatment (if applicable)*	• Nature and frequency of dose limiting toxicities (DLTs) and other adverse events (AEs), pharmacodynamic (PD) and pharmacokinetic (PK) profile
• To assess the safety and tolerability profile of RO7172508 *and with obinutuzumab pretreatment (if applicable)*	• Incidence, nature and severity of AEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Secondary	
• To establish the IV and SC pharmacokinetics of RO7172508 given as monotherapy *and with obinutuzumab pretreatment (if applicable)*	The PK profiles and parameters derived for RO7172508 including where appropriate and when data allow, the parameters listed below: • Maximum concentration (C_{max}) • Time of maximum concentration (T_{max})

Objectives	Endpoints
	• Clearance (CL) or apparent clearance (CL/F) (dependent on route of administration) • Volume of distribution *at steady state* (V_{ss}) • Area under the curve (AUC) • Half-life ($t_{1/2}$) • Other PK parameters may be determined, as deemed appropriate
• To assess the incidence of anti-drug antibodies (ADAs) against RO7172508 *and with obinutuzumab pretreatment (if applicable)*	• Presence or absence and titer of ADAs
• To characterize PD effects and duration of PD response for multiple doses and schedules of RO7172508 administration	• Changes in frequency, activation status and spatial distribution of tumor infiltrating lymphocytes (TILs).
• To assess preliminary anti-tumor activity of RO7172508.	• Objective response rate (ORR) • Disease control rate (DCR); defined as rate of response [RR] + stable disease [SD] • Duration of response (DOR) • Progression-free survival (PFS) (on-treatment) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria by Investigator's assessment.

OVERALL DESIGN

Study BP40092 is a first-in-human, open-label, multicenter, dose-escalation, Phase I clinical study to determine the maximum-tolerated dose (MTD) and/or the optimal biological dose (OBD) as well as the optimal schedule for intravenous (IV) and subcutaneous (SC) administrations of RO7172508 as monotherapy in participants with locally advanced and/or metastatic carcinoembryonic antigen (CEA)-positive solid tumors who have progressed on standard of care (SOC) treatment, are intolerant to SOC, and/or are non-amenable to SOC.

Study Design

The study will be conducted in two parts.

Part I of the study will consist of an IV single participant cohort/multiple-ascending dose-escalation to evaluate the safety of RO7172508 at doses that are expected to be sub-therapeutic. The starting-dose has been determined by an integrated approach, whereby the in vitro data (of both RO7172508 and *cibisatamab*) and clinical data of *cibisatamab* have been considered. RO7172508 will be administered IV every 3 weeks (Q3W), in up to approximately 5 participants with high-CEA expression in their tumor (i.e., ≥ 20% of tumor cells with immunohistochemistry [IHC] 2+ and/or 3+). Intra-participant dose-escalation is allowed up to the maximum dose achieved in Part I.

Part II is a multiple participant cohort/multiple-ascending dose-escalation to define the MTD and/or OBD of RO7172508 administered as single agent, IV and/or SC, in participants with tumors that are expressing high as well as low-CEA (low defined as ≥ 20% of tumor cells *with the sum of any IHC intensity (1+ 2+ and 3+) and not considered CEA-High*).

The study will switch from Part I to Part II when the maximum planned dose for Part I is reached or the occurrence of a RO7172508-related Grade ≥ 2 adverse event (AE) or dose-limiting toxicity (DLT) is observed, whichever comes first. The Sponsor may decide to switch from Part I to Part II in the absence of an observed RO7172508-related Grade ≥ 2 toxicity or prior to maximum planned dose for Part I.

Treatment Groups and Duration

The investigational medicinal products (IMPs) are RO7172508*, obinutuzumab* and tocilizumab.

Part I

In Part I, RO7172508 will be administered IV Q3W with a flat dose. The starting-dose of RO7172508 will be 65 μg and the maximum dose explored will be 1.6 mg. An increment-based escalation will be utilized, with a maximum 3-fold increment from one dose-level to the next.

Each cohort will include one participant in order to minimize the number of participants treated below the therapeutically relevant dose. Each participant will be followed up for a 4-week DLT window. The DLT window is divided into a 14-day safety observation period, after which the next cohort may be opened, and a further observation period of two weeks, to assess any potential late toxicity, including up to one week after the second administration on a Q3W dosing schedule.

Part II

The starting-dose for the initiation of Part II IV dose-escalation will be determined by Part I and RO7172508 will be initially given Q3W. Dose-escalation will continue based on safety until determination of the MTD or the planned maximum dose of 400 mg. If on-target toxicity is reported predominantly in the first cycle of treatment, fractionated dosing may be implemented for the first cycle to improve tolerability.

Once the IV schedule has shown RO7172508 preliminary clinical activity, defined by partial response (PR) or better, according to RECIST v. 1.1 (Appendix 6), or the MTD has been established and is equal to or above 2 mg, the SC multiple-ascending dose-finding cohorts could be initiated. The starting-dose and regimen (QW or Q3W) for SC administration will be proposed based on the evaluation of the safety and PK data observed following IV administration but will not exceed the highest safe dose tested in the IV Q3W dose escalation; however, due to practical considerations, a minimum dose of 2 mg is defined for a single SC administration. In addition, the QW SC starting-dose will not exceed one third of the IV MTD or of the highest safe IV dose tested.

In Part II, a modified continual reassessment method with overdose control (mCRM-EWOC) will guide the dose-escalation part to determine the MTD, by using primary safety variables (e.g., DLT).

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 low probability (< 25%) that the DLT rate is above 35%.

During the dose-escalation, at least 3 evaluable participants will be treated in a staggered manner at each dose-level (1 week or more between first and second participant, 1 day or more between subsequent participants). After the third evaluable participant in each cohort has completed the 3-week DLT period, the logistic regression model will be updated with the treatment outcome (i.e., the occurrence of DLT) and a new estimate of the MTD will be derived. Further enrollment into the next cohort will only resume after the Sponsor and the Investigators have jointly decided on the next dose-escalation step. Dose-escalation decisions and dose-selection for the next cohort will be subject to clinical judgment (following review of safety and available PK and/or PD data [and not based solely on DLT information], as well as being guided by the EWOC recommendation). Built-in safety constraints are in place to prevent exposing participants to undue risk of toxicity, i.e., for Q3W dosing schedule, maximum allowable dose-increment, in absence of DLT, will be 100%; if one DLT occurs then, an increment of 50% maximum will be allowed. A new cohort of participants will be dosed at the new estimate of the MTD or the highest allowable dose based on pre-specified safety constraints, whichever is lower. The design will continue as described, assigning participants to the MTD as estimated

from all of the DLT data cumulatively, until one of the pre-defined stopping criteria is satisfied or the pre-determined sample size is reached, whichever comes first.

If deemed necessary, *at the end of dose escalation,* to further characterize the safety, PK, and/or PD profile of RO7172508 IV and/or SC, additional participants (maximum of 15 participants) may be enrolled at the doses already tested or at doses that have not been explored for the determination of the MTD but not higher than MTD. *The additional patients could be allocated to one or more doses; however, the total number will not exceed 15 participants across all doses.*

Administration of Obinutuzumab

Administration of obinutuzumab is based on the incidence of anti-drug antibodies (ADAs) or evidence of loss of exposure (LOE) in a significant number of patients treated with RO7172508. For specific details of implementation see Section 4.1.3.

Administration of Tocilizumab

Administration of tocilizumab is based on clinical presentation of cytokine release syndrome (CRS) and should follow the guidelines stated in Section 8.3.8.1.

Length of Study

Study duration for each participant in Part I or Part II will be:

Screening: Days -28 to -1.

Treatment Period: Cycle 1 Day 1 to Month 24 (may be modified if supported by emerging data).

Safety follow-up: 60 days after last treatment with RO7172508.

Survival follow-up: Every 3 months after the last treatment with RO7172508.

End of Study

The end of the study is defined as the date of the last visit of the last participant in the study globally. Because of the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor.

PARTICIPANT POPULATION

Participants in this study are patients with locally advanced and/or metastatic CEA-expressing solid tumors *with cytoplasmic and/or membranous CEA expression in ≥ 20% of cells at intensity of IHC1+ or greater.*

Inclusion/Exclusion Criteria

Inclusion Criteria

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

Informed Consent

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

Age

2. Age ≥ 18 years.

Type of Participants and Disease Characteristics

3. **For Part I** (single participant cohorts), participants with locally advanced and/or metastatic solid tumor with confirmed cytoplasmic and/or membranous high CEA expression in tumor tissue (≥ 20% of tumor cells staining with CEA IHC 2+ or 3+ intensity) is required (participants without archived tumor tissue available for testing must have a lesion amenable to biopsy). Participants must have progressed on a SOC therapy, be intolerant to SOC, and/or are non-amenable to SOC.

4. For <*12 mg dose* cohorts, serum CEA (sCEA) levels below a certain threshold is required as follows:
    - For dose cohorts 65-159 μg, a*n* sCEA level of < 22 ng/mL.
    - For dose cohorts 160-399 μg, a*n* sCEA level of < 28 ng/mL.
    - For dose cohorts 400-799 μg, a*n* sCEA level of < 44 ng/mL.
    - For dose cohorts 800-1599 μg, a*n* sCEA level of < 70 ng/mL.
    - For the dose cohort of 1.6 - *3.1* mg, a*n* sCEA level of < 123 ng/mL.
    - *For the dose cohort of 3.2 - 6.3 mg, an sCEA level of < 229 ng/mL.*
    - *For the dose cohort of 6.4 -11.9 mg, an sCEA level of < 440 ng/mL.*

    If dose fractionation is implemented, the sCEA threshold for inclusion should correspond to the dose range of the first dose administered.

    For Part II at least 3 participants in each cohort should have a baseline sCEA level ≤20 ng/ml.
5. **For Part II,** participants with locally advanced and/or metastatic solid tumor expressing cytoplasmic and/or membranous on ≥ 20% of tumor cells of high-CEA or low-CEA on archival material (or fresh biopsy when archival is not available), who have progressed on a SOC therapy, are intolerant to SOC, and/or are non-amenable to SOC. Participants must have a lesion amenable to biopsy (except participants with NSCLC, which may be enrolled with archival tissue available only). *For patients with colorectal cancer (CRC) only, the CEA assessment by IHC should be performed but the result is not required to enroll the patient.*
    - High-CEA: ≥20% of tumor cells with IHC 2+ and/or 3+
    - *L*ow-CEA: *≥ 20% of tumor cells with the sum of any IHC intensity (1+, 2+ and 3+) and not considered CEA-High*
6. Radiologically measurable disease according to RECIST v1.1.
7. Life expectancy (in the opinion of the Investigator) of ≥ 12 weeks.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1.
9. All acute toxic effects of any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade ≤ 1 or returned to baseline, except alopecia (any grade) and Grade 2 peripheral neuropathy.
10. Adequate hematological function: neutrophil count of ≥ 1.5 × 109 cells/L, platelet count of ≥ 100,000/μL, and hemoglobin ≥ 8 g/dL (4.9 mmol/L) including lymphocytes within normal limits (≥ 0.8 × 109 cells/L).
11. Adequate liver function: total bilirubin ≤ 1.5 × the upper limit of normal (ULN; excluding Gilbert's Syndrome), aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2.5 × ULN (in case of liver metastases, ≤ 5 × ULN).
12. Adequate renal function: creatinine clearance by Cockcroft Gault formula ≥ 60 mL/min for participants with, in the Investigator's judgment, serum creatinine levels that do not adequately reflect renal function.
13. Adequate lung function: vital capacity and forced expiratory volume in first second > 65% of age and body-weight predicted normal. Diffusion capacity > 55% of predicted normal.

Sex

14. Male and female participants

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

a. Female Participants

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

- Women of non-childbearing potential (WONCBP),
- Women of childbearing potential (WOCBP), who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year from screening until 2 months after the last dose of RO7172508. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, and copper intrauterine devices.
  - Have a negative pregnancy test (blood) within one week prior to the first study treatment administration (applicable to premenopausal women and women ≤ 2 years after start of menopause (menopause is defined as amenorrhea for > 2 years).

b. Male Participants

During the treatment period and for at least 2 months after the last dose of study treatment}, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom *or a* contraceptive method that result in a failure rate of < 1% per year, with partners who are WOCBP.
- Refrain from donating sperm during the study.

Exclusion Criteria

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

Medical Conditions

1. Participants with a history or clinical evidence of central nervous system (CNS) primary tumors or metastases including leptomeningeal metastases unless they have been previously treated, are asymptomatic, and have had no requirement for steroids or enzyme-inducing anticonvulsants in the last 14 days before screening.
2. Participants with non-irradiated lesions > 2 cm at critical sites (e.g., paraspinal, paratracheal) where tumor swelling induced by RO7172508 is expected to lead to significant complications.
3. Participants with another invasive malignancy in the last 2 years (with the exception of basal cell carcinoma and tumors deemed by the Investigator to be of low likelihood for recurrence).
4. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or contraindicate the use of an investigational drug, including diabetes mellitus and history of relevant pulmonary disorders.

Diagnostic Assessments

5. Uncontrolled hypertension (systolic blood pressure [SBP] > 150 mmHg and/or diastolic BP [DBP] > 100 mmHg), unstable angina, congestive heart failure New York Heart Association (NYHA) > 1, serious cardiac arrhythmia that requires treatment with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia, and history of myocardial infarction within 6 months of enrollment.
6. Active or uncontrolled infections.
7. Known hepatitis B or C (active replicating).

8. Major surgery or significant traumatic injury < 28 days prior to the first RO7172508 administration (excluding biopsies) or anticipation of the need for major surgery during study treatment.
9. Dementia or altered mental status that would prohibit informed consent.
10. Baseline corrected QT interval of > 470 ms. Participants with baseline resting bradycardia < 45 beats per minute (bpm) or baseline resting tachycardia > 100 bpm.
11. Radiotherapy within the last 28 days prior to the first RO7172508 administration with the exception of limited-field palliative radiotherapy.
12. Presence of bilateral lung lesions with either > 3 lesions per lung or ≥ 1 lesion per lung with a diameter > 3 cm *(only unequivocal lesions of >1 cm are to be counted for this criterion, unless there is miliary metastatic-type diffuse disease, then these participants are ineligible).*

Prior/Concomitant Therapy

13. Concurrent therapy with any other investigational drug (defined as treatment for which there is currently no regulatory authority-approved indication) < 28 days prior to the first RO7172508 administration.
14. Last dose with an immunostimulating or immunosuppressive therapy (e.g., interferon (IFN)-α, IFN-β, interleukin [IL]-2, etanercept, infliximab, tacrolimus, cyclosporine, or mycophenolic acid) less than 28 days prior to the first RO7172508 administration.
15. Last dose of anti-CTLA4, anti-PD-L1 or anti-PD1 less than 180 days prior to the first RO7172508 administration.
16. Expected need for regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease) within 28 days prior to the first RO7172508 administration.
17. Regular dose of corticosteroids within 28 days prior to Day 1 of this study or anticipated need for corticosteroids that exceeds prednisone 10 mg/day or equivalent within 28 days prior to the first RO7172508 administration. Inhaled and topical steroids are permitted.
18. Prior treatment with a bispecific T-cell engaging drug targeting CD3e and/or CEA.

Other Exclusions

19. Known hypersensitivity to any of the components of RO7172508.

Specific Exclusion Criteria if Pre-treatment with Obinutuzumab is Implemented

20. *Known HIV (HIV testing will be performed at screening if required by local regulations)*
21. *Positive test results for chronic HBV infection (defined as positive HBsAg serology), HBcAb indicating an active viral infection and positive test results for HCV (HCV antibody serology testing).*
22. *Participants positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV ribonucleic acid (RNA).*
23. *History of progressive multifocal leukoencephalopathy.*
24. *Active TB requiring treatment within 3 years prior to baseline.*
25. *Latent TB diagnosed during Screening.*
26. *Positive test results for human T-lymphotropic virus 1 (HTLV 1)*
27. *HTLV testing is required in participants from endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia)*
28. *Known hypersensitivity to any of the components of obinutuzumab.*

NUMBER OF PARTICIPANTS

In Part I, approximately 5 participants will be enrolled. In Part II, *up to* approximately *75* participants each dose-escalation*, including additional 15 participants* (150 participants total in both IV and SC) will be enrolled. *In case the OBD is evaluated with and without obinutuzumab, an additional 15 participants may be enrolled.*

CONCOMITANT MEDICATIONS

Permitted Therapy

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

Radiotherapy

The use of palliative radiotherapy is allowed at any time during the study, **except for:**

- Days where study drug is administered.
- During the DLT evaluation window.
  - If radiotherapy is administered during the DLT evaluation window, the participant will not be evaluable.

Participants should not receive study treatment during radiation treatment.

Prohibited Therapy

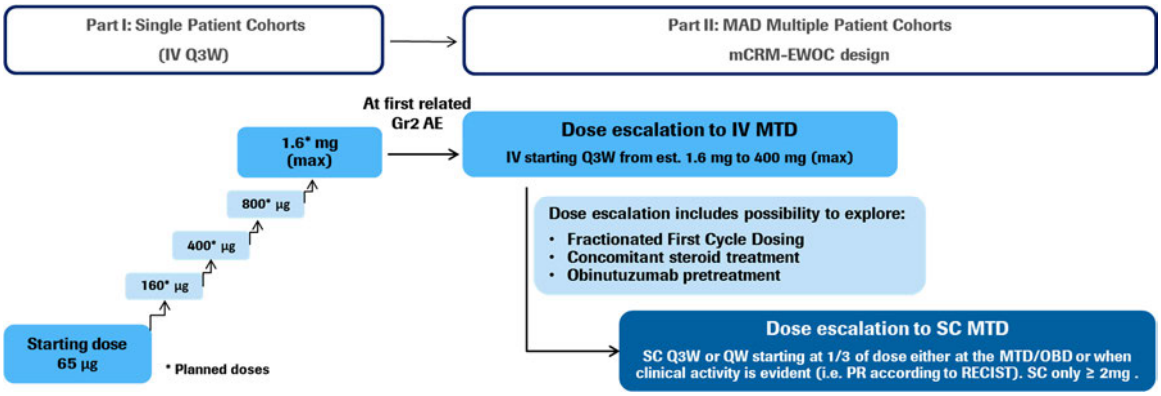
The use of the following therapies is prohibited during the study and for at least 28 days prior to initiation of study treatment (unless otherwise specified):

- Investigational or unlicensed/unapproved agents
- Immunotherapy/radio-immunotherapy
- Chemotherapy/targeted therapy
- Radiotherapy (with the exception of limited–field palliative radiotherapy).
- Biologic agents (e.g., bevacizumab)
- Chronic use of steroids (inhaled and topical steroids are permitted).
- Administration of a live, attenuated vaccine within 28 days before Cycle 1 Day 1 or anticipation that such a live attenuated vaccine will be required during the study.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in .

Figure 1 Overview of Study Design



1.3 SCHEDULE OF ACTIVITIES

The schedules of the activities (SoAs) are provided in Table 1 , Table 2, Table 3, Table 4 Table 5, *Table 6, and Table 7*.

Table 1 Part I: Single Participant Cohorts IV/Multiple-ascending Dose-escalation

Cycle (21 days)	Screening	Cycle 1 (incl. 14-day observation period)							Cycle 2—3[a]				Cycle 4 onwards[a]			End of Treatment	Safety Follow-Up	Survival Follow-Up[o]	Un-scheduled (Safety)
Day	**D-28 to D-1**	**Day 1**			**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 1**		**Day 8**	**Day 15**	**Day 1**		**Day 8**				
Assessments[a]		pre-dose	EOI *+15 mins*	2 hrs EOI *±15 mins*	24hs EOI ±2 hrs	48hrs EOI ±4 hrs			pre-dose	EOI *+15 mins*			pre-dose	EOI *+15 mins*		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (± 5 Days)	90 Days after last treatment then every 3 mths[o]	e.g. In the event of an IRR ≥G2[p]
Informed Consent[b]	X																		
Eligibility	X																		
CEA confirmation on Archival Tissue[j]	X[j]																		
Demography	X																		
Medical History	X																		
Pulmonary Function Tests[t]	X																		
Physical Examination[c]	X	X							X				X			X	X		X
Anthropometric Measurements[d]	X	X							X				X			X	X		
ECOG Performance Status	X	X							X				X			X	X		X
Vital Signs[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology[h]	X	X	X		X	X	X	X	X	X	X	X	X	X[r]	X	X	X		X
Blood Chemistry[h]	X	X			X	X	X	X	X		X	X	X		X	X	X		X
Coagulation[h]	X	X			X	X	X	X	X		X	X	X		X	X	X		X
Serology[i]	X																		
Urinalysis[h]	X	X							X				X			X	X		
Pregnancy Test[f]	X[f]								X				X				X		
ECG-12 lead[e]	X	X	X						X	X			X[e]				X		

Table 1 Part I: Single Participant Cohorts IV/Multiple-ascending Dose-escalation (cont.)

Cycle (21 days)	Screening	Cycle 1 (incl. 14-day observation period)							Cycle 2—3[a]				Cycle 4 onwards[a]			End of Treatment	Safety Follow-Up	Survival Follow-Up[o]	Un-scheduled (Safety)
Day	**D-28 to D-1**	**Day 1**			**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 1**		**Day 8**	**Day 15**	**Day 1**		**Day 8**				
Assessments[a]		pre-dose	EOI *+15 mins*	2 hrs EOI *±15 mins*	24hs EOI ±2 hrs	48hrs EOI ±4 hrs			pre-dose	EOI *±15 mins*			pre-dose	EOI *+15 mins*		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (± 5 Days)	90 Days after last treatment then every 3 mths[n o]	e.g. In the event of an IRR ≥G2[p]
Administration of RO7172508[g]		X[l]							X[g]				X[g]						
Adverse Events	X																		
Previous and Concomitant Treatments	X																		
Tumor Assessment[k]	X								X[k]				X[k]			X			
sCEA	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X		X
RO7172508 PK Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ADA to RO7172508		X					X	X	X		X	X	X			X	X		X
PD Blood Cytokines		X	X	X	X	X	X	X	X	X	X		X[n]	X[r]	X[n]	X			X[p]
IgE and Tryptase																			X[p]

Notes: ADA = anti-drug antibody; AE = adverse event; C = Cycle; CEA = carcinoembryonic antigen; D = day; discont = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; G2 = grade 2; HIV = human immunodeficiency virus; IgE = immunoglobulin E; incl = including; IRR = infusion related reaction; PD = pharmacodynamics; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; sCEA = soluble CEA.

a) All visits from Cycle 3 onwards should occur within a 3-day time window, unless otherwise indicated and all assessments or samples where indicated should be taken prior to the administration of RO7172508.

b) Informed consent must be obtained before any study-specific procedures *and may be obtained > 28 days before the start of study treatment.*

c) Physical examinations to be performed on days of treatment administration, and at the 60-day safety follow-up.

d) Weight to be recorded pre-infusion. Height to be measured at screening only.

Table 1 Part I: Single Participant Cohorts IV/Multiple-ascending Dose-escalation (cont.)

e) 12-lead ECG at screening (within one week before first dose of RO7172508). After Cycle 5, 12-lead ECG to be done only at every second cycle (i.e., C7, C9 etc.). Additional unscheduled triplicate ECG assessments should be performed in case of abnormalities and/or if clinical symptoms occur. Recording must be done prior to PK sampling.

f) Serum pregnancy test at screening, within 7 days prior to first dose, and at the safety follow-up visit; a urine pregnancy test will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. Results must be obtained and reviewed prior to administration of RO7172508.

g) All planned assessments are to be performed before administration of RO7172508. All participants in Part I of the study will receive, as a minimum, one dose of RO7172508. If there are no safety concerns, participants may receive further doses Q3W at the same dose level. Dose escalation for individual participants to the next available tolerated dose level can only proceed after a participant has tolerated their current dose for at least two cycles.

h) Hematology, blood chemistry, coagulation, and urinalysis can be performed within 24 hours (up to 72 hours if during weekend) prior to scheduled dosing. Screening results can be within 1 week prior to C1D1. Results must be obtained and reviewed prior to administration of RO7172508.

i) Serology (as per local regulations) includes HIV, hepatitis B surface antigen, total hepatitis B core antibody, hepatitis C virus antibody. Results must be obtained and reviewed prior to administration of RO7172508.

j) As part of the eligibility procedure, CEA expression will be confirmed on archival tumor material. A fresh tumor biopsy will be collected and assessed for eligibility ONLY if no archival tumor sample is available.

k) Tumor response is assessed by the Investigator per RECIST v1.1 with the use of physical examination and image-based evaluation. All measurable and evaluable lesions should be assessed and documented during the screening period, within 7 days before Cycle 3 Day 1, thereafter every 6 weeks (± 7 days) for 12 weeks, and then every 12 weeks (± 7 days) until disease progression or death. (i.e. screening, C3, C5, C7, C11, C15, C19 etc.).

l) All planned assessments are to be performed before administration of RO7172508. At least 24 hour (overnight) hospital stay required following the administration of study drug at Cycle 1 Day 1.

m) sCEA sample to be taken on Cycle 2 only.

n) Cytokines from Cycle 5 onwards, samples to be taken every second cycle up to Cycle 15 (e.g. C5, C7 etc.).

o) Survival follow-up visit to be performed 90 days (± 7 Days) after the last treatment either in person or a phone call to document any ongoing or resolved AEs, and every 3 months (± 2 weeks) thereafter for overall survival.

p) Sample to be taken only if a ≥ Grade 2 safety event is suspected to be immune-related (e.g., IRR). Refer to Table 5 for additional assessments if safety event is an IRR/CRS (≥ Grade 3) that requires tocilizumab treatment.

q) sCEA sample at screening to be taken within 14 days of Cycle 1 Day 1.

r) Samples required for Cycle 4 and Cycle 5 only.

s) Vital signs include systolic and diastolic blood pressure; pulse rate; temperature; respiratory rate and oxygen saturation.

t) Pulmonary function tests should include spirometry; forced expiratory volume (FEV1), forced vital capacity (FVC) and Diffusion capacity (DLCO).

Table 2 Part II: Multiple Participant Cohorts IV $Q3W$/Multiple Ascending Dose-Escalation

Cycle (21 days)	Screening[x]	Cycle 1 - 2							Cycle 3 - 4[a]						Cycle 5 onwards[a]				End of Treatment	Safety Follow-Up	Survival Follow-Up[q]	Unscheduled (Safety)
Day	**D-28 to D-1**	**Day 1**			**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 1**			**Day 3[p]**	**Day 8**	**Day 15**	**Day 1**		**Day 3[c, p]**	**Day 15**				
Assessments[a]		pre-dose	EOI *+15 mins*	2 hrs EOI *±15 mins*[l]	24 hrs EOI ±2 hrs	48 hrs EOI ±4 hrs			pre-dose	EOI *+15 mins*	2 hrs EOI *±15 mins*	48 hrs EOI ±1 day			pre-dose	EOI[t] *+15 mins*	48 hrs EOI ±4 hrs		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (±5 Days)	90 Days after last treatment then every 3 mths[q]	e.g. In the event of an IRR ≥G2[o]
Informed Consent[b]	X																					
Eligibility	X																					
Demography	X																					
Medical History	X																					
Pulmonary Function Tests[w]	X																					
Archival Tissue[h]	X																					
Previous and Concomitant Treatments	X																					
Adverse Events	X																					
Physical Examination	X	X							X						X				X	X		X
Anthropometric Measurements[s]	X	X							X						X				X	X		X
Vital Signs[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]	X	X	X	X		X
ECOG Performance Status	X	X							X						X				X	X		
ECG-12 lead[d]	X	X	X						X	X					X[d]					X		
Pregnancy Test[e]	X								X						X					X		
Hematology[f]	X	X	X		X	X	X	X	X	X		X	X	X	X	X[t]	X	X	X	X		X

Table 2 Part II: Multiple Participant Cohorts IV $Q3W$/Multiple Ascending Dose-Escalation (cont.)

Cycle (21 days)	Screening[x]	Cycle 1 - 2							Cycle 3 - 4[a]						Cycle 5 onwards[a]				End of Treatment	Safety Follow-Up	Survival Follow-Up[q]	Unscheduled (Safety)
Day	**D-28 to D-1**	**Day 1**			**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 1**			**Day 3[p]**	**Day 8**	**Day 15**	**Day 1**		**Day 3[c, p]**	**Day 15**				
Assessments[a]		pre-dose	EOI *+15 mins*	2 hrs EOI *±15 mins*	24 hrs EOI ±2 hrs	48 hrs EOI ±4 hrs			pre-dose	EOI *+15 mins*	2 hrs EOI *±15 mins*	48 hrs EOI +/- 1 day			pre-dose	EOI[t] *+15 mins*	48 hrs EOI ±4 hrs		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (± 5 Days)	90 Days after last treatment then every 3 mths[q]	e.g. In the event of an IRR ≥G2[o]
Blood Chemistry[f]	X	X			X	X	X	X	X			X	X	X	X		X	X	X	X		X
Coagulation[f]	X	X			X	X	X	X	X			X	X	X	X		X	X	X	X		X
Serology[r]	X																					
Urinalysis[f]	X	X							X						X				X	X		
Fresh Tumor Biopsy[g]	X[g]						X[g]												X[g]			
Tumor Assessment[i]	X								X[i]						X[i]				X			
Tumor Kinetics[l]	X																					
Administration of obinutuzumab[x]	*x*[x]																					
Obinutuzumab PK Sample[x]	*x*[x]	*x*					*x*[u]		X						*x*[y]				*x*			
ADA to obinutuzumab	*x*														*x*[y]							
Administration of RO7172508[j]		X[j]							X[j]						X[j]							
RO7172508 PK Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X
ADA to RO7172508		X					X	X	X				X	X	X				X	X		X
sCEA	*x*[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X		X

Table 2 Part II: Multiple Participant Cohorts IV $Q3W$/Multiple Ascending Dose-Escalation (cont.)

Cycle (21 days)	Screening	Cycle 1 - 2							Cycle 3 - 4[a]						Cycle 5 onwards[a]				End of Treatment	Safety Follow-Up	Survival Follow-Up[q]	Unscheduled (Safety)
Day	D-28 to D-1	Day 1			Day 2	Day 3	Day 8	Day 15	Day 1			Day 3[p]	Day 8	Day 15	Day 1		Day 3[c, p]	Day 15				
Assessments[a]		pre-dose	EOI +15 mins	2 hrs EOI ±15 mins	24 hrs EOI ±2 hrs	48 hrs EOI ±4 hrs			pre-dose	EOI +15 mins	2 hrs EOI ±15 mins	48 hrs EOI ±1 day			pre-dose	EOI[t] +15 mins	48 hrs EOI ±4 hrs		incl. early discont. visit e.g. progressive disease	60 Days after last treatment (± 5 Days)	90 Days after last treatment then every 3 mths[q]	e.g. In the event of an IRR ≥G2[o]
PD Blood Flow Cytometry		X			x		X		X				X		x^{aa}				x			
PD Blood Cytokines		X	X	X	X	X	X	X	X	X	X	X	X		X[m]	X[t]	X[m]		X			X[o]
TCR Vβ[k]		X[k]													X[k]							
CtDNA/tumor markers		X[k]													X[n]							
Clinical Genotyping		X[u]																				
RBR Sample (DNA)		X[u]																				
RBR Sample (RNA)		X[u]													X[n]							
IgE & Tryptase																						X[o]

Notes: ADA = anti-drug antibody; AE = adverse event; C = Cycle; CEA = carcinoembryonic antigen; ct = circulating tumor; D = day; discont = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; G2 = grade 2; HIV = human immunodeficiency virus; IgE = immunoglobulin E; incl = including; IRR = infusion related reaction; PD = pharmacodynamics; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; sCEA = soluble CEA; TCR = T cell receptor.

a) All visits from Cycle 3 onwards should occur within a 3-day time window, unless otherwise indicated and all assessments or samples where indicated should be taken prior to the administration of RO7172508.

b) Informed consent must be obtained before any study-specific procedures *and may be obtained > 28 days before the start of study treatment.*

c) Visit to be done only every second cycle after Cycle 5. (i.e. C7, C9 etc.).

d) 12-lead ECG at screening (within one week before first dose of RO7172508). After Cycle 4, 12-lead ECG to be done only at every second cycle (i.e. Cycle 6, Cycle 8 etc.). Additional unscheduled ECG assessments in triplicate should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done prior to PK sampling.

Table 2 Part II: Multiple Participant Cohorts IV $Q3W$/Multiple Ascending Dose-Escalation (cont.)

e) Serum pregnancy test at screening, within 7 days prior to first dose, and at the safety follow-up visit; a urine pregnancy test will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. Results must be obtained and reviewed prior to administration of RO7172508.

f) Hematology, blood chemistry, coagulation, and urinalysis can be performed within 24 hours (up to 72 hours if during weekend) prior to scheduled dosing. Screening results can be within 1 week prior to C1D1. Results must be obtained and reviewed prior to administration of RO7172508.

g) Tumor biopsy samples will be collected during screening, once during the study treatment period at Cycle 2 Day 8 and optionally at the end of treatment visit ONLY if the reason for discontinuation is progressive disease. If a fresh biopsy is performed for screening purposes, this can be used as the baseline sample.

h) As part of the eligibility procedure, CEA expression will be confirmed on archival tumor material*, with the exception of CRC participants*. If no archival tumor sample is available, fresh sample will be collected and be assessed (the same sample would constitute as baseline screening sample if participant is enrolled). Archival tissue should be submitted for additional biomarker assessments for all participants (if available).

i) Tumor response is assessed by the Investigator per RECIST V1.1 with the use of physical examination and image-based evaluation. All measurable and evaluable lesions should be assessed and documented during the screening period, within 7 days before Cycle 3 Day 1, thereafter every 6 weeks (± 7 days) for 12 weeks, and then every 12 weeks (± 7 days) until disease progression or death. (i.e. screening, C3, C5, C7, C11, C15, C19 etc.).

j) All planned assessments are to be performed before administration of RO7172508. At least 24 hours (overnight) hospital stay required following administration of study drug at Cycle 1 Day 1.

k) TCR Vβ *and CtDNA/tumor marker* samples to be drawn at Cycle 1 Day 1 predose (baseline) and Cycle 5 Day 1 predose.

l) To allow estimation of tumor growth rate before start of treatment, an exploratory assessment of tumor kinetics will be made by comparing post-treatment scans with at least 2 pretreatment scans not older than 12 weeks prior to C1D1, if available. One of the pretreatment scans will be the study baseline scan taken during screening and the second will be within the preceding 12 weeks.

m) Cytokines from Cycle 5 onwards, samples to be taken every second cycle up to Cycle 15 (e.g. C5, C7 etc.).

n) RBR (RNA) and CtDNA/tumor markers samples to be taken on Cycle 5 only.

o) Sample to be taken only if ≥ Grade 2 the safety event is suspected to be immune-related (e.g., IRR). Refer to Table 5 for additional assessments if safety event is an IRR/CRS (≥ Grade 3) that requires tocilizumab treatment. *Any biopsy samples or results done as part of standard of care can be shared with the Sponsor if applicable.*

p) The Day 3 visit may be adjusted +/- 1 day depending on safety and PD data. The visit optimal timepoint will be communicated to the Investigators for consistency and should occur ± 4 hrs from each complete day of administration (i.e. 24hrs ± 4hrs; 48 hrs ± 4hrs; OR 72hrs ± 4hrs).

q) Survival follow-up visit to be performed 90 days (± 7 Days) after the last treatment either in person or a phone call to document any ongoing or resolved AEs, and every 3 months (± 2 weeks) thereafter for overall survival.

Table 2 Part II: Multiple Participant Cohorts IV $Q3W$/Multiple Ascending Dose-Escalation (cont.)

r) Serology (as per local regulations) includes HIV, hepatitis B surface antigen, total hepatitis B core antibody, hepatitis C virus antibody. Results must be obtained and reviewed prior to administration of RO7172508.

s) Weight to be recorded pre-infusion. Height to be measured at screening only.

t) Required for Cycle 5 only.

u) Samples to be collected only in Cycle 1

v) Vital signs include systolic and diastolic blood pressure; pulse rate; temperature; respiratory rate and oxygen saturation.

w) Pulmonary function tests should include spirometry; forced expiratory volume (FEV1), forced vital capacity (FVC) and Diffusion capacity (DLCO).

x) Refer to Table 6 in the event obinutuzumab pre-treatment is implemented for specific additional assessments during the screening period.

y) Obinutuzumab ADA and PK samples to be taken only in Cycle 5 and 7 before administration of RO7172508.

z) sCEA to be assessed for enrollment in cohorts with RO7172508 doses < 12 mg.

aa) PD blood flow cytometry to be taken from Cycle 5 onwards only at Cycles 8,12 and 16 at predose

Table 3 Part II: Multiple Participant Cohorts SC QW/Multiple Ascending Dose-Escalation

Cycle (21 days)	Screening[x]	Cycle 1								Cycle 2 - 4[a]				Cycle 5 onwards[a]				End of Treatment	Safety Follow-Up	Survival Follow-Up[r]	Unscheduled (Safety)
Day	**D-28 to D-1**	**Day 1**	**Day 2**	**Day 3**	**Day 5[t]**	**Day 8**	**Day 10[o]**	**Day 15**	**Day 17**	**Day 1**	**Day 5[t]**	**Day 8**	**Day 15**	**Day 1**	**Day 5[ct]**	**Day 8**	**Day 15**				
Assessments[a]		pre-dose	24 hrs post dose (±2 hrs)	48 hrs post dose (±4 hrs)	96 hrs post dose (±5 hrs)	pre-dose	48 hrs post dose (±4 hrs)	pre-dose	48 hrs post dose (±4 hrs)	pre-dose	96 hrs post dose (±1 day)	pre-dose	pre-dose	pre-dose	96 hrs post dose (±5 hrs)	pre-dose	pre-dose	incl. early discont. visit (e.g. progressive disease)	60 days after last treatment	90 Days after last treatment then every 3 mths[r]	e.g. In the event of an IRR ≥G2[n]
Informed Consent[b]	X																				
Eligibility	X																				
Demography	X																				
Medical History	X																				
Pulmonary Function Tests[w]	X																				
Archival Tissue[h]	X																				
Previous and Concomitant Treatments	X																				
Adverse Events	X																				
Physical Examination	X	X								X				X				X	X		X
Anthropometric Measurements[q]	X	X								X				X					X		
Vital Signs[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ECOG Performance Status	X	X								X				X				X	X		X
ECG-12 lead[d]	X	X			X					X	X			X[d]				X	X		
Pregnancy Test[e]	X									X				X					X		

Table 3 Part II: Multiple Participant Cohorts SC QW/Multiple Ascending Dose-Escalation (cont.)

Cycle (21 days)	Screening[x]	Cycle 1								Cycle 2 - 4[a]				Cycle 5 onwards[a]				End of Treatment	Safety Follow-Up	Survival Follow-Up[r]	Unscheduled (Safety)
Day	**D-28 to D-1**	**Day 1**	**Day 2**	**Day 3**	**Day 5[t]**	**Day 8**	**Day 10[o]**	**Day 15**	**Day 17**	**Day 1**	**Day 5[t]**	**Day 8**	**Day 15**	**Day 1**	**Day 5[c,t]**	**Day 8**	**Day 15**				
Assessments[a]		pre-dose	24 hrs post dose (±2 hrs)	48 hrs post dose (±4 hrs)	96 hrs post dose (±5 hrs)	pre-dose	48 hrs post dose (±4 hrs)	pre-dose	48 hrs post dose (±4 hrs)	pre-dose	96 hrs post dose (±1 day)	pre-dose	pre-dose	pre-dose	96 hrs post dose (±5 hrs)	pre-dose	pre-dose	incl. early discont. visit (e.g. progressive disease)	60 days after last treatment	90 Days after last treatment then every 3 mths[r]	e.g. In the event of an IRR ≥G2[n]
Hematology[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
Blood Chemistry[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X
Coagulation[f]	X	X	X	X	X	X	X	X	X	X		X	X	X				X	X		X
Serology[u]	X																				
Urinalysis[f]	X	X								X				X				X	X		X
Fresh Tumor Biopsy[g]	X											X[g]						X[g]			
Tumor Assessment[i]	X									X[i]				X[i]				X			
Tumor Kinetics[J]	X																				
Administration of obinutuzumab[x]	X[x]																				
Obinutuzumab PK Sample[xy]	X[x]	*x*				*x*				*x*				X[y]				*x*			
ADA to obinutuzumab[xy]	X[x]													X[y]							
Administration of RO7172508[s]		X[s]				X[s]		X[s]		X[s]		X[s]	X[s]	X[s]		X[s]	X[s]				
RO7172508 PK Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ADA to RO7172508		X				X		X		X		X	X	X				X	X		X
sCEA	*x*[z]	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X		X
PD Blood Flow Cytometry		X	*x*			X	*x*			X		X		*x*[aa]				*x*			
PD Blood Cytokines		X	X	X	X	X	X	X	X	X	X	X	X[p]	X[k]	X[k]			X			X[n]
TCR Vβ[l]		X												X[l]							
CtDNA/tumor markers		X												X[m]							

Table 3 Part II: Multiple Participant Cohorts SC QW/Multiple Ascending Dose-Escalation (cont.)

Cycle (21 days)	Screening[x]	Cycle 1								Cycle 2 - 4[a]				Cycle 5 onwards[a]				End of Treatment	Safety Follow-Up	Survival Follow-Up[r]	Unscheduled (Safety)
Day	**D-28 to D-1**	**Day 1**	**Day 2**	**Day 3**	**Day 5[t]**	**Day 8**	**Day 10[o]**	**Day 15**	**Day 17**	**Day 1**	**Day 5[t]**	**Day 8**	**Day 15**	**Day 1**	**Day 5[ct]**	**Day 8**	**Day 15**				
Assessments[a]		pre-dose	24 hrs post dose (±2 hrs)	48 hrs post dose (±4 hrs)	96 hrs post dose (±5 hrs)	pre-dose	48 hrs post dose (±4 hrs)	pre-dose	48 hrs post dose (±4 hrs)	pre-dose	96 hrs post dose (±1 day)	pre-dose	pre-dose	pre-dose	96 hrs post dose (±5 hrs)	pre-dose	pre-dose	incl. early discont. visit (e.g. progressive disease)	60 days after last treatment	90 Days after last treatment then every 3 mths[r]	e.g. In the event of an IRR ≥G2[n]
Clinical Genotyping		X																			
RBR Sample (DNA)		X																			
RBR Sample (RNA)		X												X[m]							
IgE and Tryptase																					X[n]

Notes: ADA = anti-drug antibody; AE = adverse event; C = Cycle; CEA = carcinoembryonic antigen; ct = circulating tumor; D = day; discont = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; G2 = grade 2; HIV = human immunodeficiency virus; IgE = immunoglobulin E; incl = including; IRR = infusion related reaction; PD = pharmacodynamics; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; sCEA = soluble CEA; TCR = T cell receptor.

a) All visits from Cycle 3 onwards should occur within a 3-day time window, unless otherwise indicated and all assessments or samples where indicated should be taken prior to the administration of RO7172508.
b) Informed consent must be obtained before any study-specific procedures *and may be obtained > 28 days before the start of study treatment*.
c) Day 5 visit to be done only every second cycle after Cycle 5. (i.e. C7, C9 etc.).
d) 12-lead ECG at screening (within one week before first dose of RO7172508). After Cycle 4, 12-lead ECG to be done only at every second cycle (i.e. Cycle 6, Cycle 8 etc.). Additional unscheduled ECG assessments in triplicate should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done prior to PK sampling.
e) Serum pregnancy test at screening, within 7 days prior to first dose, and at the safety follow-up visit; a urine pregnancy test will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. Results must be obtained and reviewed prior to administration of RO7172508.

Table 3 Part II: Multiple Participant Cohorts QW SC/Multiple Ascending Dose-Escalation (cont.)

f) Hematology, blood chemistry, coagulation, and urinalysis can be performed within 24 hours (up to 72 hours if during weekend) prior to scheduled dosing. Screening results can be within 1 week prior to C1D1. Results must be obtained and reviewed prior to administration of RO7172508.

g) Tumor biopsy samples will be collected during screening, once during the study treatment period at Cycle 2 Day 8 and optionally at the end of treatment visit ONLY if the reason for discontinuation is progressive disease. If a fresh biopsy is performed for screening purposes, this can be used as the baseline sample.

h) As part of the eligibility procedure, CEA expression will be confirmed on archival tumor material, *with the exception of CRC participants*. If no archival tumor sample is available, fresh sample will be collected and be assessed (the same sample would constitute as baseline screening sample if participant is enrolled). Archival tissue should be submitted for additional biomarker assessments for all participants (if available).

i) Tumor response is assessed by the Investigator per RECIST V1.1 with the use of physical examination and image-based evaluation. All measurable and evaluable lesions should be assessed and documented during the screening period, within 7 days before Cycle 3 Day 1, thereafter every 6 weeks (± 7 days) for 12 weeks, and then every 12 weeks (± 7 days) until disease progression or death. (i.e. screening, C3, C5, C7, C11, C15, C19 etc.).

j) To allow estimation of tumor growth rate before start of treatment, an exploratory assessment of tumor kinetics will be made by comparing post treatment scans with at least 2 pretreatment scans not older than 12 weeks prior to C1D1, if available. One of the pretreatment scans will be the study baseline scan taken during screening and the second will be within the preceding 12 weeks.

k) Cytokines from Cycle 5 onwards, samples to be taken every second cycle up to Cycle 15 (e.g. C5, C7 etc.).

l) TCR Vβ samples to be drawn at Cycle 1 Day 1 predose (baseline) and Cycle 5 Day 1 predose.

m) RBR (RNA) and CtDNA/tumor markers samples to be taken on Cycle 5 only.

n) Sample to be taken only if a ≥ Grade 2 safety event is suspected to be immune-related (e.g., IRR). Refer to Table 5 for additional assessments if safety event is an IRR/CRS (≥ Grade 3) that requires tocilizumab treatment. *Any biopsy samples or results done as part of standard of care can be shared with the Sponsor if applicable.*

o) Visit may be omitted depending on emerging safety data for SC and/or fractionated dosing regimens after discussion between Investigators and the Sponsor.

p) Cytokines sample to be taken on Cycle 2 only.

q) Weight to be recorded pre-infusion. Height to be measured at screening only.

r) Survival follow-up visit to be performed 90 days (± 7 Days) after the last treatment either in person or a phone call to document any ongoing or resolved AEs, and every 3 months (± 2 weeks) thereafter for overall survival.

s) All planned assessments are to be performed before administration of RO7172508.

t) Day 5 visit optional if it falls on a non-working day *and can be performed +/- 1 day*.

u) Serology (as per local regulations) includes HIV, hepatitis B surface antigen, total hepatitis B core antibody, hepatitis C virus antibody. Results must be obtained and reviewed prior to administration of RO7172508.

v) Vital signs include systolic and diastolic blood pressure; pulse rate; temperature; respiratory rate and oxygen saturation.

Table 3 Part II: Multiple Participant Cohorts QW SC/Multiple Ascending Dose-Escalation (cont.)

w) Pulmonary function tests should include spirometry; forced expiratory volume (FEV1), forced vital capacity (FVC) and Diffusion capacity (DLCO).

x) Refer to Table 6 in the event obinutuzumab pre-treatment is implemented for specific additional assessments during the screening period.

y) Obinutuzumab ADA and PK samples to be taken only in Cycle 5 and 7 before administration of RO7172508.

z) sCEA to be assessed for enrollment in cohorts with RO7172508 doses < 12 mg.

aa) PD blood flow cytometry to be taken from Cycle 5 onwards only at Cycles 8,12 and 16 at predose

Table 4 Part II: Fractionated Dosing IV Cohort *for Q3W*

Cycle (21 days)	Screen-ing[w]	Cycle 1											Cycle 2 - 4[a]						Cycle 5 onwards[a]				End of Treat-ment	Safety Follow-Up	Survival Follow-Up[r]	Un-scheduled (Safety)
Day	D-28 to D-1	Day 1			Day 2	Day 3	Day 8		Day 9[p]	Day 15		Day 16[p]	Day 1			Day 3	Day 8	Day 15	Day 1		Day 3[c]	Day 15				
Assessments[a]		pre-dose	EOI +15 mins	2 hrs EOI ±15 mins	24 hrs EOI ±2 hrs	48 hrs EOI ±4 hrs	pre-dose	EOI +15 mins	24 hrs EOI ±2 hrs	pre-dose	EOI +15 mins	24 hrs EOI ±2 hrs	pre-dose	EOI +15 mins	2 hrs EOI ±15 mins	48 hrs EOI ±4 hrs			pre-dose	EOI[t] +15 mins	48 hrs EOI ±4 hrs		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (±5 Days)	90 Days after last treatment then every 3 mths[r]	e.g. In the event of an IRR ≥G2[o]
Informed Consent[b]	X																									
Eligibility	X																									
Demography	X																									
Medical History	X																									
Pulmonary Function Tests[v]	X																									
Archival Tissue[h]	X																									
Previous and Concomitant Treatments	X																									
Adverse Events	X																									
Physical Examination	X	X											X						X				X	X		X
Anthropometric Measurements[q]	X	X											X						X				X	X		X
Vital Signs[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]	X	X	X	X		X

Table 4 Part II: Fractionated Dosing IV Cohort *for Q3W* (cont.)

Cycle (21 days)	Screen-ing[w]	Cycle 1											Cycle 2 - 4[a]						Cycle 5 onwards[a]				End of Treat-ment	Safety Follow-Up	Survival Follow-Up[r]	Un-scheduled (Safety)
Day	**D-28 to D-1**	**Day 1**			**Day 2**	**Day 3**	**Day 8**		**Day 9[p]**	**Day 15**		**Day 16[p]**	**Day 1**			**Day 3**	**Day 8**	**Day 15**	**Day 1**		**Day 3[c]**	**Day 15**				
Assessments[a]		pre-dose	EOI +15 mins	2 hrs EOI ±15 mins	24 hrs EOI ±2 hrs	48 hrs EOI ±4 hrs	pre-dose	EOI +15 mins	24 hrs EOI ±2 hrs	pre-dose	EOI +15 mins	24 hrs EOI ±2 hrs	pre-dose	EOI +15 mins	2 hrs EOI ±15 mins	48 hrs EOI ±4 hrs			pre-dose	EOIt +15 mins	48 hrs EOI ±4 hrs		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (±5 Days)	90 Days after last treatment then every 3 mths[r]	e.g. In the event of an IRR ≥G2[o]
ECOG Performance Status	X	X											X						X				X	X		
ECG-12 lead[d]	X	X	X										X	X					X[d]					X		
Pregnancy Test[e]	X												X						X					X		
Hematology[f]	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X[t]	X	X	X	X		X
Blood Chemistry[f]	X	X			X	X	X		X	X		X	X			X	X	X	X		X	X	X	X		X
Coagulation[f]	X	X			X	X	X		X	X		X	X			X	X	X	X		X	X	X	X		X
Serology[s]	X																									
Urinalysis[f]	X	X											X						X				X	X		
Fresh Tumor Biopsy[g]	X																X[g]						X[g]			
Tumor Assessment[i]	X												X[i]						X[i]				X			
Tumor Kinetics[l]	X																									
Administration of obinutuzumab[w]	X[w]																									
Obinutuzumab PK Sample[wx]	X[w]	*x*					*x*						*x*						X[x]				*x*			
ADA to obinutuzumab[wx]	X[w]																		X[x]							
Administration of RO7172508 [j]		X[j]					X[j]			X[j]			X[j]						X[j]							

Table 4 Part II: Fractionated Dosing IV Cohort for $Q3W$ (cont.)

Cycle (21 days)	Screen-ing[w]	Cycle 1											Cycle 2 - 4[a]							Cycle 5 onwards[a]				End of Treat-ment	Safety Follow-Up	Survival Follow-Up[r]	Un-scheduled (Safety)
Day	D-28 to D-1	Day 1			Day 2	Day 3	Day 8		Day 9[p]	Day 15		Day 16[p]	Day 1			Day 3	Day 8	Day 15		Day 1		Day 3[c]	Day 15				
Assessments[a]		pre-dose	EOI +15 mins	2 hrs EOI ±15 mins	24 hrs EOI ±2 hrs	48 hrs EOI ±4 hrs	pre-dose	EOI +15 mins	24 hrs EOI ±2 hrs	pre-dose	EOI +15 mins	24 hrs EOI ±2 hrs	pre-dose	EOI +15 mins	2 hrs EOI ±15 mins	48 hrs EOI ±4 hrs			pre-dose	EOI t +15 mins	48 hrs EOI ±4 hrs		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (±5 Days)	90 Days after last treatment then every 3 mths[r]	e.g. In the event of an IRR ≥G2[o]
RO7172508 PK Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]	X	X	X	X	X		X
ADA to RO7172508		X					X			X			X				X	X	X					X	X		X
sCEA	x^y	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X		X
PD Blood Flow Cytometry		X			x		X		x				X				X		x^z					x			
PD Blood Cytokines		X	X	X	X	X	X	X		X	X		X	X	X	X	X		X[m]	X[t]	X[m]		X			X[o]	
TCR Vβ[k]		X																	X[k]								
CtDNA/tumor markers		X																	X[n]								
Clinical Genotyping		X																									
RBR Sample (DNA)		X																									
RBR Sample (RNA)		X																	X[n]								
IgE and Tryptase																										X[o]	

Table 4 Part II: Fractionated Dosing IV Cohort *for Q3W* (cont.)

Notes: ADA = anti-drug antibody; AE = adverse event; C = Cycle; CEA = carcinoembryonic antigen; ct = circulating tumor; D = day; discont = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; G2 = grade 2; HIV = human immunodeficiency virus; IgE = immunoglobulin E; incl = including; IRR = infusion related reaction; PD = pharmacodynamics; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; sCEA = soluble CEA; TCR = T cell receptor.

a) All visits from Cycle 3 onwards should occur within a 3-day time window, unless otherwise indicated and all assessments or samples where indicated should be taken prior to the administration of RO7172508.
b) Informed consent must be obtained before any study-specific procedures *and may be obtained > 28 days before the start of study treatment*.
c) Day 3 visit to be done only every second cycle after Cycle 5. (i.e. C7, C9 etc.).
d) 12-lead ECG at screening (within one week before first dose of RO7172508). After Cycle 4, 12-lead ECG to be done only at every second cycle (i.e. Cycle 6, Cycle 8 etc.). Additional unscheduled ECG assessments in triplicate should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done prior to PK sampling.
e) Serum pregnancy test at screening, within 7 days prior to first dose, and at the safety follow-up visit; a urine pregnancy test will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. Results must be obtained and reviewed prior to administration of RO7172508.
f) Hematology, blood chemistry, coagulation, and urinalysis can be performed within 24 hours (up to 72 hours if during weekend) prior to scheduled dosing. Screening results can be within 1 week prior to C1D1. Results must be obtained and reviewed prior to administration of RO7172508.
g) Tumor biopsy samples will be collected during screening, once during the study treatment period at Cycle 2 Day 8 and optionally at the end of treatment visit ONLY if the reason for discontinuation is progressive disease. If a fresh biopsy is performed for screening purposes, this can be used as the baseline sample.
h) As part of the eligibility procedure, CEA expression will be confirmed on archival tumor material, *with the exception of CRC participants*. If no archival tumor sample is available, fresh sample will be collected and be assessed (the same sample would constitute as baseline screening sample if participant is enrolled). Archival tissue should be submitted for additional biomarker assessments for all participants (if available).
i) Tumor response is assessed by the Investigator per RECIST V1.1 with the use of physical examination and image-based evaluation. All measurable and evaluable lesions should be assessed and documented during the screening period, within 7 days before Cycle 3 Day 1, thereafter every 6 weeks (± 7 days) for 12 weeks, and then every 12 weeks (± 7 days) until disease progression or death. (i.e. screening, C3, C5, C7, C11, C15, C19 etc.).
j) All planned assessments are to be performed before administration of RO7172508. At least 24 hours (overnight) hospital stay required following administration of study drug at Cycle 1 Day 1.

Table 4 Part II: Fractionated Dosing IV Cohort *for Q3W* (cont.)

k) TCR Vβ samples to be drawn at Cycle 1 Day 1 predose (baseline) and Cycle 5 Day 1 predose.

l) To allow estimation of tumor growth rate before start of treatment, an exploratory assessment of tumor kinetics will be made by comparing post treatment scans with at least 2 pretreatment scans not older than 12 weeks prior to C1D1, if available. One of the pretreatment scans will be the study baseline scan taken during screening and the second will be within the preceding 12 weeks.

m) Cytokines from Cycle 5 onwards, samples to be taken every second cycle up to Cycle 15 (e.g. C5, C7 etc.).

n) RBR (RNA) and CtDNA/tumor markers samples to be taken on Cycle 5 only.

o) Sample to be taken only if a ≥ Grade 2 safety event is suspected to be immune-related (e.g., ≥ G2 IRR). Refer to Table 5 for additional assessments if safety event is an IRR/CRS (≥ Grade 3) that requires tocilizumab treatment. *Any biopsy samples or results done as part of standard of care can be shared with the Sponsor if applicable.*

p) Visit may be omitted depending on emerging safety data for fractionated dosing regimens after discussion between Investigators and the Sponsor.

q) Weight to be recorded pre-infusion. Height to be measured at screening only.

r) Survival follow-up visit to be performed 90 days (± 7 Days) after the last treatment either in person or a phone call to document any ongoing or resolved AEs, and every 3 months (± 2 weeks) thereafter for overall survival.

s) Serology (as per local regulations) includes HIV, hepatitis B surface antigen, total hepatitis B core antibody, hepatitis C virus antibody. Results must be obtained and reviewed prior to administration of RO7172508.

t) Required for Cycle 5 only.

u) Vital signs include systolic and diastolic blood pressure; pulse rate; temperature; respiratory rate and oxygen saturation.

v) Pulmonary function tests should include spirometry; forced expiratory volume (FEV1), forced vital capacity (FVC) and Diffusion capacity (DLCO).

w) Refer to Table 6 in the event obinutuzumab pre-treatment is implemented for specific additional assessments during the screening period.

x) Obinutuzumab ADA and PK samples to be taken only in Cycle 5 and 7 before administration of RO7172508.

y) sCEA to be assessed for enrollment in cohorts with RO7172508 doses < 12 mg.

z) PD blood flow cytometry to be taken from Cycle 5 onwards only at Cycles 8,12 and 16 at predose

Table 5 Schedule of Assessments for IRR and CRS related to RO7172508

Assessment/Procedure	Pre-TCZ Treatment (within 24 hours)[g]	TCZ Administration	Post-TCZ Treatment[c]		
			End of infusion *(±15 mins)*	2 hours *(±15 mins)*	24 hours *(±2 hrs)*
TCZ Administration (8 mg/kg)		X			
Vital signs[a]	X		Measure at least every 6 hours until resolution to baseline[f]		
Pressor documentation[b]	X		Record at least every 6 hours until pressors are discontinued[f]		
FiO_2 or L/min of 100% O2	X		Record at least every 6 hours until patient on room air[f]		
Local Laboratory Assessments					
Hematology	X		X	X	X
Blood chemistry	X		X	X	X
Coagulation	X		X	X	X
Infection workup[d]	X				
Central Laboratory Assessments					
Plasma cytokines[e]	X	X[h]	X	X	X

aPTT = activated partial thromboplastin time; CRP = C-reactive protein; CRS = cytokine release syndrome; eCRF = electronic Case Report Form; INR = international normalized ratio; IL-6 = interleukin 6; LDH = lactate dehydrogenase; PT = prothrombin time; TCZ = tocilizumab.

Record abnormalities or worsened clinically significant abnormalities on the Adverse Event eCRF.

a) Vital signs include systolic and diastolic blood pressure; pulse rate; temperature; respiratory rate and oxygen saturation.

b) Document vasopressor type and dose in the concomitant medication eCRF if applicable.

c) If TCZ dose is repeated, follow Schedule of Assessments following the second TCZ dose.

d) Includes assessment for bacterial, fungal, and viral infections *as clinically indicated*.

Table 5 Schedule of Assessments for IRR and CRS related to RO7172508 (cont.)

e) Includes the same cytokine analysis as per PD Blood Cytokines.

f) The maximum and minimum values for any 24-hour period should be recorded in the clinical database if applicable.

g) Assessments to be performed in addition to an unscheduled (safety) visit. If the unscheduled (safety) or end of infusion local laboratory and cytokine assessments have been performed within 24 hours, then duplicated samples for pre-TCZ treatment do not need to be repeated.

h) To be taken within 2 hours before TCZ treatment

Table 6 *Screening Schedule of Assessments with Obinutuzumab Pretreatment*

	Screening Period with Obinutuzumab Pre-treatment				*Cycle 1*
Day	***Day -28 to Day -8***	***Day -7***	***Day -6***	***Day -5 to Day -1***	***Day 1***
Assessments					*See relevant SoA depending on applicable schedule for ongoing assessments*
Informed Consent[a]	*x*				
Eligibility	*x*				
Demography	*x*				
Medical History	*x*				
Pulmonary Function Tests[b]	*x*				
Archival Tissue[c]	*x*				
Previous and Concomitant Treatments	*x*	*x*	*x*	*x*	
Adverse Events	*x*	*x*	*x*	*x*	
Physical Examination	*x*	*x*	*x*		
Anthropometric Measurements[d]	*x*				
Vital Signs[e]	*x*	*x*	*x*	*x*	
ECOG Performance Status	*x*			*x*	
ECG-12 lead[f]	*x*			*x*	
Pregnancy Test[g]	*x*			*x*	
Hematology[h]	*x*	*x*		*x*	
Blood Chemistry[h]	*x*	*x*		*x*	
Coagulation[h]	*x*	*x*		*x*	

Table 6 Screening Schedule of Assessments with Obinutuzumab Pretreatment (cont.)

	Screening Period with Obinutuzumab Pre-treatment				Cycle 1
Day	**Day -28 to Day -8**	**Day -7**	**Day -6**	**Day -5 to Day -1**	**Day 1**
Assessments					*See relevant SoA depending on applicable schedule for ongoing assessments*
Serology[i]	*x*				
Urinalysis[h]	*x*				
Fresh Tumor Biopsy[j]	*x*[j]				
Tumor Assessment[k]	*x*				
Tumor Kinetics[l]	*x*				
Administration of obinutuzumab[m]		*x*	*x*		
Obinutuzumab PK Sample		*x*[n]	*x*[p]		
ADA to Obinutuzumab		*x*[n]			
sCEA	*x*[o]				
PD Blood Flow Cytometry		*x*[n]			
PD Blood Cytokines		*x*[n]			

ADA = anti-drug antibody; AE = adverse event; C = Cycle; CEA = carcinoembryonic antigen; ct = circulating tumor; D = day; discont = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; G2 = grade 2; HIV = human immunodeficiency virus; IgE = immunoglobulin E; incl = including; IRR = infusion related reaction; PD = pharmacodynamics; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; sCEA = soluble CEA; TCR = T cell receptor.

Table 6 *Screening Schedule of Assessments with Obinutuzumab Pretreatment (cont.)*

a Informed consent must be obtained before any study-specific procedures and may be obtained > 28 days before the start of study treatment..

b Pulmonary function tests should include spirometry; forced expiratory volume (FEV1), forced vital capacity (FVC) and Diffusion capacity (DLCO).

c As part of the eligibility procedure, CEA expression will be confirmed on archival tumor material, with the exception of CRC participants. If no archival tumor sample is available, fresh sample will be collected and be assessed (the same sample would constitute as baseline screening sample if participant is enrolled). Archival tissue should be submitted for additional biomarker assessments for all participants (if available).

d Weight to be recorded pre-infusion. Height to be measured at screening only.

e Vital signs include systolic and diastolic blood pressure; pulse rate; temperature; respiratory rate and oxygen saturation.

f 12-lead ECG at screening (within one week before obinutuzumab pre-treatment and within 5 days of the first dose of RO7172508). Additional unscheduled ECG assessments in triplicate should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done prior to PK sampling.

g Serum pregnancy test at screening, within 7 days prior to first dose of obinutuzumab. Results must be obtained and reviewed prior to administration of obinutuzumab. Prior to the first dose of RO7172508 a urine pregnancy test will be performed. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

h Hematology, blood chemistry, coagulation, and urinalysis can be performed within 24 hours (up to 72 hours if during weekend) prior to scheduled dosing. Screening results can be within 1 week prior to C1D1 but after obinutuzumab pre-treatment. Results must be obtained and reviewed prior to administration of RO7172508 or obinutuzumab.

i Serology (as per local regulations) includes HIV, hepatitis B surface antigen, total hepatitis B core antibody, hepatitis C virus antibody. Results must be obtained and reviewed prior to administration of obinutuzumab.

j Tumor biopsy samples will be collected during screening. If a fresh biopsy is performed for screening purposes, this can be used as the baseline sample. This biopsy should be taken BEFORE obinutuzumab is administered.

k Tumor response is assessed by the Investigator per RECIST V1.1 with the use of physical examination and image-based evaluation. All measurable and evaluable lesions should be assessed and documented during the screening period before obinutuzumab pre-treatment.

l To allow estimation of tumor growth rate before start of treatment an exploratory assessment of tumor kinetics will be made by comparing post treatment scans with at least 2 pre-treatment scans not older than 12 weeks prior to C1D1 if available. One of the pre-treatment scans will be the study baseline scan taken during screening and the second will be within the preceding 12 weeks.

m Obinutuzumab to be administered either on Day-7 (2000 mg) or on Day-7 and Day-6 (1000 mg each day). If obinutuzumab is given only on one day, then the schedule for Day-7 should be followed including an end of infusion sample.

n Samples should be taken BEFORE obinutuzumab is administered.

o sCEA to be assessed for enrollment in cohorts with RO7172508 doses < 12 mg.

p Sample to be taken end of infusion only

Table 7 *Schedule of Assessments Part II: Multiple Participant Cohorts SC Q3W*

Cycle (21 days)	*Screening*[x]	*Cycle 1 - 2*						*Cycle 3 - 4*[a]				*Cycle 5 onwards*[a]			*End of Treatment*	*Safety Follow-Up*	*Survival Follow-Up*[q]	*Unscheduled (Safety)*
Day	*D-28 to D-1*	*Day 1*	*Day 2*	*Day 3*	*Day 5*	*Day 8*	*Day 15*	*Day 1*	*Day 3*[p]	*Day 8*	*Day 15*	*Day 1*	*Day 3*[c, p]	*Day 15*				
Assessments[a]		*pre-dose*	*24 hrs +/- 2 hrs*	*48 hrs +/- 4 hrs*	*+/- 1 day*			*pre-dose*	*48 hrs +/- 1 day*			*pre-dose*	*48hrs +/- 4 hrs*		*incl. early discont. visit (e.g. progressive disease)*	*60 Days after last treatment (+/- 5 Days)*	*90 Days after last treatment then every 3 mths*[q]	*e.g. In the event of an IRR ≥G2*[o]
Informed Consent[b]	*x*																	
Eligibility	*x*																	
Demography	*x*																	
Medical History	*x*																	
Pulmonary Function Tests[w]	*x*																	
Archival Tissue[h]	*x*																	
Previous and Concomitant Treatments	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Adverse Events	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Physical Examination	*x*	*x*						*x*				*x*			*x*	*x*		*x*
Anthropometric Measurements[s]	*x*	*x*						*x*				*x*			*x*	*x*		*x*
Vital Signs[v]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		*x*

Table 7 Schedule of Assessments Part II: Multiple Participant Cohorts SC Q3W (cont.)

Cycle (21 days)	Screening[x]	Cycle 1 - 2						Cycle 3 - 4[a]				Cycle 5 onwards[a]			End of Treatment	Safety Follow-Up	Survival Follow-Up[q]	Unscheduled (Safety)
Day	D-28 to D-1	Day 1	Day 2	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3[p]	Day 8	Day 15	Day 1	Day 3[c, p]	Day 15				
Assessments[a]		pre-dose	24 hrs +/- 2 hrs	48 hrs +/- 4 hrs	+/- 1 day			pre-dose	48 hrs +/- 1 day			pre-dose	48hrs +/- 4 hrs		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (+/- 5 Days)	90 Days after last treatment then every 3 mths[q]	e.g. In the event of an IRR ≥G2[o]
ECOG Performance Status	x	x						x				x			x	x		
ECG-12 lead[d]	x	x						x				x[d]				x		
Pregnancy Test[e]	x							x				x				x		
Hematology[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Blood Chemistry[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Coagulation[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Serology[r]	x																	
Urinalysisf	x	x						x				x			x	x		
Fresh Tumor Biopsy[g]	x[g]					x[g]									x[g]			
Tumor Assessment[i]	x							x[i]				x[i]			x			
Tumor Kinetics[l]	x																	
Administration of obinutuzumab[x]	x[x]																	

Table 7 Schedule of Assessments Part II: Multiple Participant Cohorts SC Q3W (cont.)

Cycle (21 days)	Screening[x]	Cycle 1 - 2						Cycle 3 - 4[a]				Cycle 5 onwards[a]			End of Treatment	Safety Follow-Up	Survival Follow-Up[q]	Unscheduled (Safety)
Day	D-28 to D-1	Day 1	Day 2	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3[p]	Day 8	Day 15	Day 1	Day 3[c, p]	Day 15				
Assessments[a]		pre-dose	24 hrs +/- 2 hrs	48 hrs +/- 4 hrs	+/- 1 day			pre-dose	48 hrs +/- 1 day			pre-dose	48hrs +/- 4 hrs		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (+/- 5 Days)	90 Days after last treatment then every 3 mths[q]	e.g. In the event of an IRR ≥G2[o]
Obinutuzumab PK Sample[x]	x[x]	x				x[u]		x				x[y]			x			
ADA to obinutuzumab[x]	x[x]											x[y]						
Administration of RO7172508[j]		x[j]						x[j]				x[j]						
RO7172508 PK Sample		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
ADA to RO7172508		x			x	x	x	x		x	x	x			x	x		x
sCEA	x	x[z]	x	x	x	x	x	x	x	x	x	x	x		x	x		x
PD Blood Flow Cytometry		x	x			x		x		x		x[aa]			x			
PD Blood Cytokines		x	x	x	x	x	x		x	x		x[m]	x[m]		x			x[o]
TCR Vβ[k]		x[k]										x[k]						
CtDNA/tumor markers		x[k]						x				x[n]						
Clinical Genotyping		x[u]																
RBR Sample (DNA)		x[u]																

Table 7 Schedule of Assessments Part II: Multiple Participant Cohorts SC Q3W (cont.)

Cycle (21 days)	Screening[x]	Cycle 1 - 2						Cycle 3 - 4[a]				Cycle 5 onwards[a]			End of Treatment	Safety Follow-Up	Survival Follow-Up[q]	Unscheduled (Safety)
Day	D-28 to D-1	Day 1	Day 2	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3[p]	Day 8	Day 15	Day 1	Day 3[c, p]	Day 15				
Assessments[a]		pre-dose	24 hrs +/- 2 hrs	48 hrs +/- 4 hrs	+/- 1 day			pre-dose	48 hrs +/- 1 day			pre-dose	48hrs +/- 4 hrs		incl. early discont. visit (e.g. progressive disease)	60 Days after last treatment (+/- 5 Days)	90 Days after last treatment then every 3 mths[q]	e.g. In the event of an IRR ≥G2[o]
RBR Sample (RNA)		x[u]										x[n]						
IgE & Tryptase																		x[o]

ADA = anti-drug antibody; AE = adverse event; C = Cycle; CEA = carcinoembryonic antigen; ct = circulating tumor; D = day; discont = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; G2 = grade 2; HIV = human immunodeficiency virus; IgE = immunoglobulin E; incl = including; IRR = infusion related reaction; PD = pharmacodynamics; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; sCEA = soluble CEA; TCR = T cell receptor.

a *All visits from Cycle 3 onwards should occur within a 3-day time window, unless otherwise indicated and all assessments or samples where indicated should be taken prior to the administration of RO7172508.*

b *Informed consent must be obtained before any study-specific procedures and can be obtained > 28 days from the start of screening.*

c *Visit to be done only every second cycle after Cycle 5. (i.e. C7, C9 etc.).*

d *12-lead ECG at screening (within one week before first dose of RO7172508). After Cycle 4, 12-lead ECG to be done only at every second cycle (i.e. Cycle 6, Cycle 8 etc.). Additional unscheduled ECG assessments in triplicate should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done prior to PK sampling.*

e *Serum pregnancy test at screening, within 7 days prior to first dose, and at the safety follow-up visit; a urine pregnancy test will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. Results must be obtained and reviewed prior to administration of RO7172508.*

f *Hematology, blood chemistry, coagulation, and urinalysis can be performed within 24 hours (up to 72 hours if during weekend) prior to scheduled dosing. Screening results can be within 1 week prior to C1D1. Results must be obtained and reviewed prior to administration of RO7172508.*

Table 7 Schedule of Assessments Part II: Multiple Participant Cohorts SC Q3W (cont.)

g	*Tumor biopsy samples will be collected during screening, once during the study treatment period at Cycle 2 Day 8 and optionally at the end of treatment visit ONLY if the reason for discontinuation is progressive disease. If a fresh biopsy is performed for screening purposes, this can be used as the baseline sample.*
h	*As part of the eligibility procedure, CEA expression will be confirmed on archival tumor material, with the exception of CRC participants. If no archival tumor sample is available, fresh sample will be collected and be assessed (the same sample would constitute as baseline screening sample if participant is enrolled). Archival tissue should be submitted for additional biomarker assessments for all participants (if available).*
i	*Tumor response is assessed by the Investigator per RECIST V1.1 with the use of physical examination and image-based evaluation. All measurable and evaluable lesions should be assessed and documented during the screening period, within 7 days before Cycle 3 Day 1, thereafter every 6 weeks (± 7 days) for 12 weeks, and then every 12 weeks (± 7 days) until disease progression or death. (i.e. screening, C3, C5, C7, C11, C15, C19 etc.).*
j	*All planned assessments are to be performed before administration of RO7172508. At least 24 hours (overnight) hospital stay required following administration of study drug at Cycle 1 Day 1.*
k	*TCR Vβ and CtDNA/tumor marker samples to be drawn at Cycle 1 Day 1 predose (baseline) and Cycle 5 Day 1 predose.*
l	*To allow estimation of tumor growth rate before start of treatment, an exploratory assessment of tumor kinetics will be made by comparing post-treatment scans with at least 2 pretreatment scans not older than 12 weeks prior to C1D1, if available. One of the pretreatment scans will be the study baseline scan taken during screening and the second will be within the preceding 12 weeks.*
m	*Cytokines from Cycle 5 onwards, samples to be taken every second cycle up to Cycle 15 (e.g. C5, C7 etc.).*
n	*RBR (RNA) and CtDNA/tumor markers samples to be taken on Cycle 5 only.*
o	*Sample to be taken only if ≥ Grade 2 the safety event is suspected to be immune-related (e.g., IRR). Refer to Table 5 for additional assessments if safety event is an IRR/CRS (³ Grade 3) that requires tocilizumab treatment. Any biopsy samples or results done as part of standard of care can be shared with the Sponsor if applicable.*
p	*The Day 3 visit may be adjusted +/- 1 day depending on safety and PD data. The visit optimal timepoint will be communicated to the Investigators for consistency and should occur ± 4 hrs from each complete day of administration (i.e. 24hrs ± 4hrs; 48 hrs ± 4hrs; OR 72hrs ± 4hrs).*
q	*Survival follow-up visit to be performed 90 days (± 7 Days) after the last treatment either in person or a phone call to document any ongoing or resolved AEs, and every 3 months (± 2 weeks) thereafter for overall survival.*
r	*Serology (as per local regulations) includes HIV, hepatitis B surface antigen, total hepatitis B core antibody, hepatitis C virus antibody. Results must be obtained and reviewed prior to administration of RO7172508.*
s	*Weight to be recorded pre-infusion. Height to be measured at screening only.*
t	*Required for Cycle 5 only.*
u	*Samples to be collected only in Cycle 1*
v	*Vital signs include systolic and diastolic blood pressure; pulse rate; temperature; respiratory rate and oxygen saturation.*
w	*Pulmonary function tests should include spirometry; forced expiratory volume (FEV1), forced vital capacity (FVC) and Diffusion capacity (DLCO).*

Table 7 Schedule of Assessments Part II: Multiple Participant Cohorts SC Q3W (cont.)

x	*Refer to Table 6 in the event obinutuzumab pre-treatment is implemented for specific additional assessments during the screening period.*
y	*Obinutuzumab ADA and PK samples to be taken only in Cycle , 5 and 7 before administration of RO7172508.*
z	*sCEA to be assessed for enrollment in cohorts with RO7172508 doses < 12 mg.*
aa	*PD blood flow cytometry to be taken from Cycle 5 onwards only at Cycles 8,12 and 16 at predose*

2. INTRODUCTION

2.1 STUDY RATIONALE

RO7172508 is a novel T-cell bispecific (TCB) antibody that targets carcinoembryonic antigen (CEA) expressed on tumor cells and cluster of differentiation 3 (CD3) epsilon chain (CD3e) present on T-cells.

Despite great progress in recent years, management of patients with many types of advanced solid tumors remains highly challenging. There has been renewed interest over the last few years in engaging the immune system to fight cancer. One approach currently in development is to activate T-cells against the tumor by using TCBs. The Sponsor has developed a novel TCB (RO7172508) that targets human CEA on tumor cells and CD3 on T-cells, which results in selective T-cell-mediated killing of cancerous CEA-expressing cells. CEA–related cell adhesion molecule 5 (CEACAM5) or CD66e, is a protein with molecular weight of 180–200 kDa that belongs to the CEACAM superfamily. High expression of CEA is found in various tumor types (Thompson et al 1991), including colorectal cancer, pancreatic cancer, gastric cancer, non-small cell lung cancer (NSCLC), head and neck cancer, and breast cancer among others, whereas low expression of CEA was found in small–cell lung cancer and glioblastoma (RO7172508 Investigator's Brochure). RO7172508 will be used in indications where significant subsets of patients have tumors expressing CEA.

The clinical proof-of-concept was demonstrated with *cibisatamab* (*RO6958688*, CEA-TCB), a TCB antibody targeting CEA currently in clinical development, which induced objective radiological responses both as a single agent and in combination with a programmed death-ligand 1 (PD-L1) checkpoint inhibitor atezolizumab with an acceptable safety profile (Study BP29541 [NCT02324257], Study WP29945 [NCT02650713]). RO7172508 differentiates from *cibisatamab* by having a different binding CEA domain with increased affinity to CEA exhibiting tumor cell lysis in cells with lower CEA expression level and a prolonged half-life. RO7172508 is therefore expected to show enhanced anti-tumor activity, resulting in an increased response rate in high-CEA-expressing tumors when compared to *cibisatamab*, and enabling treatment of low-CEA-expressing tumors which are not targeted by *cibisatamab*.

The aim of the current study is to define the safety profile of RO7172508 when used as a single agent, generate pharmacokinetic (PK), pharmacodynamics (PD), and efficacy data that will allow selection of an optimal route of administration and schedule for further development.

The development of anti-drug antibodies (ADAs) can result in a partial or complete loss of exposure and is thought to be mainly mediated by the stimulation of B-cells, which leads to generation of antibody-producing plasma cells. The use of obinutuzumab as a pre-treatment (if needed) to inhibit or attenuate ADA responses by depletion of B-cells has been implemented in this study and is supported by nonclinical and clinical studies further described in Section 2.2.2. For the benefit/risk assessment of obinutuzumab pre-treatment, please refer to Section 2.3.

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

2.2 BACKGROUND

2.2.1 Background on RO7172508

RO7172508 is a tumor-targeted, T-cell engaging, bispecific antibody that induces T-cell-mediated killing of tumors expressing CEA. RO7172508 contains a humanized CEA binder that binds to the A3-B3 domain of CEA with high monovalent affinity (K_d 90 pM). This is the major differentiating characteristic of this antibody relative to *cibisatamab*, which contains a humanized and stabilized CEA binder that binds to the B3 domain of CEA with an affinity of K_d 16 nM. Binding of RO7172508 to tumor cells and T-lymphocytes resulted in secretion of cytotoxic granules and ultimately, tumor cell lysis (killing). Upon TCB-mediated activation, T-cells undergo proliferation and expand at sites of tumor cell killing and, by release of pro-inflammatory cytokines, attract more immune cells into the tumor which leads to increased effector-to-target cell ratio within tumors.

There is no suitable pharmacologically relevant animal model to assess the toxicity of RO7172508; therefore, in vivo toxicity studies have not been performed. Instead, an integrated approach incorporating in vitro data (of both RO7172508 and *cibisatamab*) and clinical activity data of *cibisatamab* was used to define the starting-dose for the entry-into-human study. Results from in vitro studies on human cells using the most sensitive test systems and assay conditions yielded a starting-dose for RO7172508 of 65 μg for this study (see Section 4.3).

A detailed description of the additional in vitro studies, the chemistry, pharmacology, and safety of RO7172508 is provided in the Investigator's Brochure.

2.2.2 Obinutuzumab

RO7172508 may induce the production of ADAs that could result in the complete or partial loss of exposure. Obinutuzumab, a humanized and glycoengineered Type II anti-CD20 monoclonal antibody that recognizes the CD20 antigen present on normal and malignant B-cells. Obinutuzumab is approved for the use in untreated and relapsed/refractory follicular lymphoma as well as untreated chronic lymphocytic leukemia. The use of obinutuzumab has demonstrated effective B-cell depletion following administration in cynomolgus monkeys (Mössner et al 2010) and patients with B-cell malignancies (Salles et al 2012; Cartron et al 2014). The use of obinutuzumab as a pre-treatment to inhibit or attenuate ADA responses in participants with solid tumors is supported by nonclinical and clinical studies. Pre-clinically, obinutuzumab pre-treatment resulted in strong suppression of de novo antibody responses while protective humoral memory responses remained intact both in human CD20 transgenic mice and cynomolgus monkeys. In Studies BP28920 (RO6895882; Phase I), BP29435 (RO6895882 + atezolizumab; Phase Ib) and BP29541 (cibisatamab; Phase I), obinutuzumab pre-treatment effectiveness was confirmed as pre-treated patients did not lose exposure of the investigational compounds. For the benefit/risk assessment of obinutuzumab pre-treatment, please refer to Section 2.3.

For more details on obinutuzumab, please refer to the obinutuzumab IB.

2.2.3 Background on Tocilizumab (RO4877533, ACTEMRA®, ROACTEMRA®)

Tocilizumab blocks IL-6 from binding to its receptor, both in membrane-bound and soluble states (Singh et al 2011). With a primary indication for juvenile idiopathic arthritis (JIA), tocilizumab is approved by the Food and Drug Administration (FDA) for children as young as 2 years. It is also approved for adults with rheumatoid arthritis and for Castleman disease in Japan. Tocilizumab has been extensively studied in adults, with 8 randomized controlled trials treating more than 2000 patients (Singh et al 2011) and in children in phase 1 to phase 3 trials for JIA (Woo et al 2005, Yokota et al 2005, De Benedetti et al 2012).

In patients with severe CRS associated with T cell–engaging therapies, IL-6 levels peak during maximal T cell proliferation. A growing body of evidence suggests that IL-6 blockade by tocilizumab result in rapid, dramatic reversal of life-threatening CRS in patients treated with T cell engaging therapies (Grupp et al 2013, Teachey et al 2013). Whereas tocilizumab is typically dosed every 2 to 4 weeks, extended treatment is not necessary in the management of CRS, which is self-limited and in most cases reported to require a single administration in order to control the clinical signs of CRS after treatment with T cell engaging agents. Tocilizumab was approved for the treatment of CAR-T cell induced CRS in the US only since August 2017 (Actemra USPI).

Since CRS is a potential risk for RO7172508, tocilizumab will be administered if required, for the management of severe CRS (Table 17).

2.3 BENEFIT/RISK ASSESSMENT

The bispecific nature of RO7172508 brings immune cells into the proximity of tumor cells to exert their effector function, which has been a challenge for other classes of immunomodulatory compounds that often rely on pre-existing infiltration of immune cells for clinical activity. In pre-clinical models, RO7172508 has consistently demonstrated superior efficacy relative to *cibisatamab* suggesting the potential to expand the indications that could benefit from immunotherapies compared to *cibisatamab*, which has already shown objective clinical responses in high-CEA-expressing tumors.

The nature of adverse events (AEs) for RO7172508 is expected to be similar to *cibisatamab*, a T-cell, bispecific antibody targeting CEA which is currently in clinical development (Study BP29541). The potential AEs are: infusion-related reactions; cytokine-release syndrome, isolated pyrexia, diarrhea, events associated with tumor inflammation/tumor flare affecting organs related to the tumor site such as tumor pain, edema, impaired function of the affected organ, such as dyspnea, hypoxia, and increased levels of liver function enzymes, colitis, enteritis; immunoglobulin E (IgE)-mediated hypersensitivity reactions (theoretical risk for all biologics); risk of immunogenicity and potential safety impact (theoretical risk for all biologics); skin exfoliation; hematotoxicities; central nervous system disorders. In addition, given pre-clinical data regarding the staining of pneumocytes, signs of lung inflammation (dyspnea, hypoxia, pneumonitis) cannot be excluded even in participants without lung lesions.

Administration of monoclonal antibodies may cause a spectrum of symptoms, such as fever, chills, dizziness, hypertension, hypotension, dyspnea, restlessness, sweating, flushing, skin rash, tachycardia, tachypnoea, headache, tumor pain, nausea, and/or vomiting. Typically these symptoms are reported as infusion-related reactions (IRRs) when they occur during or shortly after the first or second infusion, or within 24 hours after study drug administration.

Symptoms of IRRs and CRS, during or after infusion of RO7172508, may be indistinguishable from each other and might be life-threatening. CRS is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, dyspnea, and renal, coagulation, hepatic and neurologic disorders; CRS is caused by the release of cytokines from cells (Lee et al 2014). Severe CRS may be associated with other clinical sequelae such as disseminated intravascular coagulation and capillary leak syndrome. Standard of care for severe or life threatening CRS resulting from immune-based therapy has not been established, especially in solid tumors.

In case of IRR/CRS, the recommended management is detailed in Table 17.

The activity of RO7172508 at the tumor site leads to the destruction of the tumor cells and tumor inflammation/flare. Given this mechanism of action, AEs associated with tumor inflammation are expected. These AEs are expected to occur shortly following RO7172508 administration and can affect organ systems with the location of the tumor lesions. These events might be life-threatening especially in case of critical location of the tumor (respiratory tract) or extensive tumor size.

Because of a higher affinity to CEA of RO7172508 compared to *cibisatamab*, the severity of adverse reactions may be higher; however, the difference in the potency has been taken into account in the evaluation of the starting-dose proposed in this study. Stringent risk mitigation measures, including required appropriate organ function at baseline (cardiac, pulmonary, liver, hematologic function), close monitoring of participants, especially around the first infusion (including 24-hour hospitalization after the first infusion), staggered enrollment, dose-escalation rules and detailed instructions regarding management of specific AEs are designed to minimize risks. Overall, these potential risks are considered manageable and acceptable in the context of anticipated benefit.

Risk mitigation has been considered in the study design and management of potential AEs is described in *Section 8.3.8 of the protocol and* the RO7172508 Investigator's Brochure.

There is a potential risk for RO7172508 to induce the production of ADAs. ADA formation against RO7172508 can potentially reduce its efficacy by blocking CEA or CD3e targeting and/or potentially result in symptomatic hypersensitivity reactions, in particular immune complex reactions. Therefore, Part II of the BP40092 study allows obinutuzumab pretreatment to attenuate the formation of ADAs if a predefined number of patients experience a loss of exposure to RO7172508 (see Section 4.1.3).

If obinutuzumab pretreatment is introduced as a way to mitigate ADA formation and subsequent loss of exposure, the safety profile of RO7172508 given after obinutuzumab will be carefully monitored. Only if the safety profile of RO7172508 after obinutuzumab pretreatment is shown to be acceptable and comparable to RO7172508 alone (i.e., without obinutuzumab pretreatment if applicable) will the Sponsor consider investigating obinutuzumab pretreatment in further development.

On the basis of all available information, the Sponsor concluded that there is an acceptable preliminary benefit-risk balance for the clinical investigation of RO7172508 in participants with locally advanced and/or metastatic CEA–positive solid tumors who have progressed on standard of care (SOC) treatment, are intolerant to SOC, and/or are non-amenable to SOC.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 8.

Table 8 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the maximum-tolerated dose (MTD) and/or the optimal biological dose (OBD) for intravenous (IV) and subcutaneous (SC) administrations of RO7172508 as monotherapy *and with obinutuzumab pre-treatment (if applicable)*	• Nature and frequency of dose-limiting toxicities (DLTs) and other AEs, PD and PK profile
• To assess the safety and tolerability profile of RO7172508 *and with obinutuzumab pre-treatment (if applicable)*	• Incidence, nature and severity of AEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Secondary	
• To establish the IV and SC pharmacokinetics of RO7172508 given as monotherapy *and with obinutuzumab pre-treatment (if applicable)*	The PK profiles and parameters derived for RO7172508 including where appropriate and when data allow, the parameters listed below: • Maximum concentration (C_{max}) • Time of maximum concentration (T_{max}) • Clearance (CL) or apparent clearance (CL/F) (dependent on route of administration) • Volume of distribution *at steady state* (V_{ss}) • Area under the curve (AUC) • Half-life ($t_{1/2}$) • Other PK parameters may be determined, as deemed appropriate.
• To assess the incidence of anti-drug antibodies (ADAs) against RO7172508 *with obinutuzumab pre-treatment (if applicable)*	• Presence or absence and titer of ADAs
• To characterize PD effects and duration of PD response for multiple doses and schedules of RO7172508 administration	• Changes in frequency, activation status and spatial distribution of tumor infiltrating lymphocytes (TILs).

Table 8 Objectives and Endpoints (cont.)

Objectives	Endpoints
Secondary (cont.)	
• To assess preliminary anti-tumor activity of RO7172508.	• Objective response rate (ORR) • Disease control rate (DCR); defined as rate of response (RR) + stable disease (SD) • Duration of response (DOR) • Progression-free survival (PFS) (on-treatment) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria by Investigator's assessment
Tertiary/Exploratory	
• To further characterize PD effects and duration of PD response for multiple doses and schedules of RO7172508 administration • To assess dose and exposure response relationship of RO7172508 and PD biomarkers and clinical endpoints	• Duration of immune activation (changes in peripheral blood immune cells and TILs, cytokines) after repeated administrations of RO7172508. • Absolute numbers and changes from baseline of immune cells (including but not limited to activated CD8+ T-cells) in peripheral blood and tumor biopsies. • Absolute levels and changes from baseline for cytokines (including but not limited to soluble CD25 [sCD25]) in peripheral blood. • Gene expression profile changes on tumor biopsies following treatment. • Changes in CEA tumor expression. • Absolute levels and changes from baseline of soluble tumor markers (including but not limited to CEA, etc.) in peripheral blood.

Table 8 Objectives and Endpoints (cont.)

Objectives	Endpoints
Tertiary/Exploratory (cont.)	
• To investigate potential prognostic/predictive biomarkers	• Absolute number, frequency and activation status of immune cells (including but not limited to CD8+ T-cells) in peripheral blood and/or tumor biopsies at baseline. • Absolute expression levels of cytokines (including but not limited to sCD25) in peripheral blood at baseline. • Absolute levels of soluble tumor markers (including but not limited to serum CEA [sCEA]) at baseline. • Gene expression profile on tumor biopsies at baseline. • Mismatch repair (MMR)/microsatellite instability (MSI) status and tumor mutations on archival tissue and whole genome.
• To further assess preliminary anti-tumor activity of RO7172508.	• PFS, objective response, DOR, and DCR according to immune modified RECIST (iRECIST). • Overall survival (OS).
• To estimate depth and duration of response on target lesion size due to RO7172508 and the effect on the risk of appearance of new lesions during treatment by tumor kinetic modeling	• Sum of lesion diameter from computed tomography (CT) scans
• To assess ADA specificity	• Development of ADAs directed against either the CEA or CD3 binding moiety.
• To make a preliminary assessment of the efficacy of tocilizumab (Actemra®/RoActemra®) in ameliorating the symptoms of severe CRS following RO7172508 treatment, if data allows.	• Changes in the nature and severity of CRS following administration of tocilizumab for severe CRS.
• *To assess the incidence of anti-drug antibodies (ADAs) against obinutuzumab (if applicable)*	• *Presence or absence and titer of ADAs* • *Serum concentration of obinutuzumab*

4. STUDY DESIGN

4.1 OVERALL DESIGN

An overview of the study design is provided in Section 1.2.

Study BP40092 is a first-in-human, open-label, multicenter, dose-escalation, Phase I clinical study to determine the maximum-tolerated dose (MTD) and/or the optimal biological dose (OBD) as well as the optimal schedule for intravenous (IV) and subcutaneous (SC) administrations of RO7172508 as monotherapy*, with or without obinutuzumab pre-treatment,* in participants with locally advanced and/or metastatic CEA-positive solid tumors who have progressed on SOC treatment, are intolerant to SOC, and/or are non-amenable to SOC. The study will be conducted in two parts.

PART I

Part I of the study is an IV single participant cohort/multiple-ascending dose-escalation study to evaluate the safety of RO7172508 at doses that are expected to be below a level that induces relevant biological effects. The starting-dose has been determined by an integrated approach, whereby the in vitro data (of both RO7172508 and *cibisatamab*) and clinical activity of *cibisatamab* have been considered (see Section 4.3). RO7172508 will be administered IV every 3 weeks (Q3W), in up to approximately 5 participants with confirmed cytoplasmic and/or membranous high-CEA expression in their tumor (i.e., ≥ 20% of tumor cells with CEA immunohistochemistry [IHC] 2+/3+). Intra-participant dose-escalation is allowed up to the maximum dose achieved in Part I (see Section 4.1.2).

PART II

Part II is a multiple participant cohort/multiple-ascending dose-escalation study to define the MTD and/or OBD of RO7172508 administered as single agent, IV or SC, in participants who have tumors with cytoplasmic and/or membranous CEA expression in ≥ 20% of cells at intensities greater than at least IHC 1+ on archival material (or fresh biopsy when archival is not available). The starting-dose for the initiation of the IV dose-escalation will be determined by Part I and RO7172508 will be initially given Q3W. Dose-escalation will be undertaken based on safety until determination of the MTD or the highest safe dose if MTD is not reached.

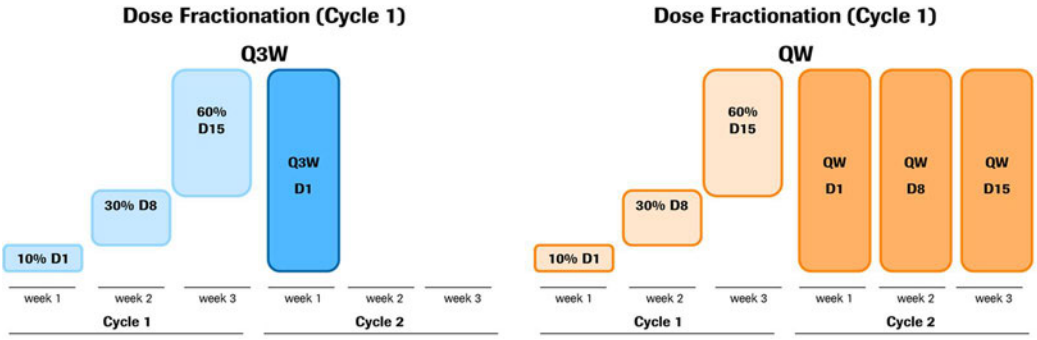
Once the IV schedule has shown RO7172508 preliminary clinical activity, defined by partial response (PR) or better, according to RECIST v. 1.1 (Appendix 6), or the MTD has been established and is equal to or above 2 mg, the SC multiple-ascending dose-finding cohorts could be initiated. The starting-dose and regimen (QW or Q3W) for SC administration will be proposed based on the evaluation of the safety and PK data observed following IV administration but will not exceed the highest safe dose tested in the IV Q3W dose escalation; however, due to practical considerations, a minimum dose of 2 mg is defined for a single SC administration. In addition, the QW SC starting-dose will not exceed one third of the IV MTD or of the highest safe IV dose tested.

Dose escalation in the SC treatment group will proceed until the SC MTD/OBD has been determined (see Section 4.1.2). *If the SC treatment group is started Q3W at a dose <6*

mg, the QW schedule can be evaluated once the dose is ≥ 6 mg. Data from this treatment group will establish if the SC route of administration, which will have a lower C_{max} than IV after first administration, can show comparable efficacy and/or comparable or improved safety profile of a TCB *either QW and/or Q3W.*

During the course of this study, the need for obinutuzumab pretreatment will be assessed based on loss of RO7172508 exposure and/or ADA-related safety events. Details, including decision criteria, are provided in Section 4.1.3 and Appendix 9. If on-target toxicity is reported predominantly in the first cycle of treatment, fractionated dosing may be implemented for the first cycle to improve tolerability. RO7172508 treatment would start with 10% of the planned dose on Cycle 1 Day 1, 30% of the planned dose on Cycle 1 Day 8 and 60% of the planned target dose on Cycle 1 Day 15, followed by the full dose treatment from Cycle 2 Day 1 onwards as described in Figure 2. By using a step-up fractionated dosing approach, it is predicted that the lower peak exposures (C_{max}) will result in lower cytokine levels to that when the full dose is given on Day 1. The fractionated dosing regimen may be adjusted depending on emerging data and in discussion with the Investigators. A similar approach to increase the dose administered during the first three weeks as applied with dose-fractionation in the Q3W treatment group, may also be employed in the once weekly (QW) treatment group. If a patient in the fractionated dose cohort experiences any adverse event that results in a delay of the next administration of RO7172508 beyond one week, the dose at which the treatment should be restarted will require agreement between the investigator and the Sponsor.

Figure 2 Fractionated Dosing Design for Q3W and QW



At least 3 evaluable participants will be treated in each cohort during the IV or SC dose-escalation regimen.

If deemed necessary*, at the end of dose escalation,* to further characterize the safety, preliminary anti-tumor activity, PK, and/or PD profile of RO7172508 (IV and/or SC) *with or without obinutuzumab pre-treatment*, additional participants (up to approximately 15 participants) may be enrolled at the doses already tested*;* or at doses that have not been explored for the determination of the MTD, but not higher than MTD*;* or the highest safe dose tested if MTD has not be determined. *The additional patients could be allocated to one or more doses; however, the total number will not exceed 15 participants across all doses. If new cohorts are opened at a dose equal to or lower than already explored, the cohorts will follow the same recruitment rules and safety windows as per dose escalation rules. Patients enrolled at dose levels that have already been assessed, will also be staggered as per dose escalation rules (i.e. at least one day between consecutive patients). If DLT events are observed, the estimated MTD and the probability of overdosing at the current recruiting cohort will be re-assessed with all available data. If the updated estimated MTD indicate that the current recruiting cohort is not safe, recruitment will be stopped.*

4.1.1 Length of the Study

Participants will be treated for up to 24 months (the treatment period may be modified if supported by emerging data) or until disease progression, loss of clinical benefit, unacceptable toxicities, or withdrawal from treatment for other reasons or death. Specifically, the duration of the study for each participant will be:

- Screening: Days -28 to -1.
- Treatment Period: Cycle 1 Day 1 to Month 24 (may be modified if supported by emerging data).
- Safety follow-up: 60 days after last treatment with RO7172508.
- Survival follow-up: Every 3 months after the last treatment with RO7172508.

4.1.2 Dose-Escalation Decision Criteria

4.1.2.1 Part I: Multiple-Ascending Dose-Escalation (Single Participant Cohorts)

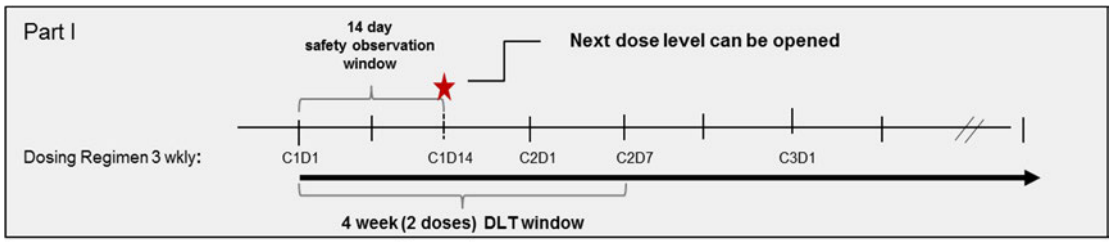
In Part I, RO7172508 will be administered IV Q3W with a flat dose. The starting-dose of RO7172508 will be 65 μg (see Section 4.3 for starting dose justification) and the maximum dose explored will be 1.6 mg. An increment-based escalation will be utilized. The first 2-step increments (up to 400 μg) are 2.5 as the first doses are considered low and sub-therapeutic. From 400 μg dose, a maximum of 3-fold increments will apply (see Section 4.3).

Thus, the 65 μg starting-dose is followed by doses of 160 μg, 400 μg, 800 μg and 1600 μg. Incremental dose-increases may be altered based on emerging PK, PD and safety data but will not exceed 3-fold.

Each cohort will include one participant in order to minimize the number of participants treated below the predicted therapeutically relevant dose. Each participant will be followed up for a 4-week dose limiting toxicity (DLT) window (Figure 3). The DLT window is divided into a 14-day safety observation period, after which the next cohort could be opened, and a further observation period of two weeks, to assess any potential late toxicity including up to one week after the second administration (i.e., total of 4 weeks).

Enrollment into the subsequent cohort will occur after the Sponsor and the Investigators have jointly decided on the next dose-escalation step. A telephone conference will be held with Investigators before a new dose-level is opened, where all available safety, PK and PD data will be evaluated. The next cohort will open if no RO7172508-related AE of Grade ≥ 2 (or DLT) is reported in a participant during the 14-day safety observation period. If a related Grade ≥ 2 AE or DLT occurs after the 14-day safety window and within the 4 weeks DLT window in a lower dose cohort, then participants at a higher dose may have their dose reduced for subsequent cycles and the switch from Part I to Part II of the study is triggered.

Figure 3 Part I: Observation and DLT Windows



Intra-participant dose-escalation is allowed in Part I. A participant (e.g., Cohort 1/Participant 1) can progressively escalate to a dose-level tolerated by subsequent cohorts if:

- Participant has completed his/her current cohort's 4-week DLT window and experienced no RO7172508-related Grade ≥ 2 AEs.

AND

- Participant in the next highest level cohort (i.e., Cohort 2/Participant 2) has safely passed his/her 14-day safety observation window.

The maximum dose-level allowed for participants in Part I will be the highest dose-level administered in Part I. Participants may continue to receive RO7172508 for up to 24 months, until disease progression, or loss of benefit (see Section 7).

Participants who undergo dose-escalation will not need to complete another 4-week DLT assessment period. All other rules for subsequent escalations still apply as noted above.

The Sponsor will switch from Part I to Part II when either a dose of 1.6 mg IV (flat dose) is reached or the occurrence of a RO7172508-related Grade ≥ 2 AE (or DLT) is observed, whichever comes first. The Sponsor may decide to switch from Part I to Part II in the absence of an observed RO7172508-related Grade ≥ 2 toxicity or prior to the dose-level reaching 1.6 mg.

4.1.2.2 Part II: Multiple-Ascending Dose-Escalation (Multiple Participant Cohorts)

A modified continual reassessment method with overdose control (mCRM-EWOC) will guide the dose-escalation to determine the MTD, by using primary safety variables (e.g., DLT). 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 two-parameter logistic regression model, which is continuously updated as additional participant information becomes available.

The prior distribution for the parameters of the DLT dose-response curve will be a mixture of informative and minimally informative components. The minimally informative component makes the design robust against unforeseen deviations from the informative component and will be constructed based on the assumed not toxic and toxic doses. For the dose toxicity relationship of the minimally informative component, it is conservatively assumed that it would be very unlikely that 10% or higher DLT rates are associated with the first dose of the monotherapy dose-escalation and that it would be very unlikely that a 25% or lower DLT rate is associated with a dose of 400 mg (additional details provided in Appendix 8). The informative component will be the posterior distribution of the CEA TCB (*cibisatamab*) monotherapy toxicity data without obinutuzumab pre-treatment, as of cutoff date 20 July 2017, approximated with a bivariate normal distribution. The two components will be mixed in a 10/90% ratio (informative prior component 10%; minimally informative component 90%). Further details are provided in Appendix 8.

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%.

- Dose-escalation to IV MTD

The Part II dose-escalation will start with a dose of 1.6 mg (flat dose) IV Q3W (Section 4.3 Dose Justification) if this dose has been reached in Part I and considered safe. In the eventuality that Part I has been stopped because of the occurrence of a RO7172508-related Grade ≥ 2 AE (or DLT) then, the starting-dose of Part II will not exceed the dose-level at which the AE that delineated the end of Part I occurred. Furthermore, the grade and type of AE will also be considered, when choosing the dose-level for Part II. In the eventuality that the Sponsor decides to initiate Part II in the absence of an observed RO7172508-related Grade ≥ 2 toxicity and prior to the dose-level reaching 1.6 mg, then the starting-dose of Part II will not exceed the highest dose tested in Part I. If the starting-dose of Part II is the same as the last dose in Part I, the participant treated at the last dose in Part I could be considered as the first participant of the cohort for Part II. If the initial dose is not tolerated, then participants for the subsequent cohort may be enrolled at a lower RO7172508 dose than the initially selected Part II starting-dose. The maximum dose of RO7172508 will be 400 mg (flat dose IV). The initial dosing regimen in Part II may also be adapted depending on emerging data in Part I.

In Part II dose-escalation, a minimum of 3 participants per cohort *will be enrolled who have a baseline sCEA level ≤20 ng/ml*. Participants within a cohort will be treated in a sequential manner with one week between the first and second participant, and at least one day between subsequent participants. However, if the first participant experiences a DLT within the first 7 days, then the time between the treatment of subsequent participants within the same cohort may be increased. The DLT evaluation window in Part II is defined as a period of 3 weeks after the first administration of RO7172508 in an IV Q3W schedule. Based on emerging data, the interval between dosing of each participant within a cohort or the DLT window may be adjusted if deemed appropriate by the Investigators and/or the Sponsor.

For each cohort, all participants will be followed through a 3-week DLT window (i.e., 21 days *after the first dose of RO7172508*). If fractionated dosing is implemented in Cycle 1 to improve tolerability, the DLT window will be extended to include the cycle where the planned target dose is administered in full i.e., *Cycle 1 Day 1 until* the end of Cycle 2. The DLT window will therefore be 6 weeks (42 days), or 8 weeks (56 days) if treatment has been delayed for no more than 14 days.

A new cohort can be opened when at least 3 evaluable participants of the previous cohort have completed the DLT window. *At least 3 evaluable participants must have a baseline sCEA level of ≤ 20 ng/ml.* If participants experience a DLT before completion of the last day of their DLT window, they will be considered as having completed their DLT window. Prior to opening a new cohort, the logistic regression model will be updated with the treatment outcome (i.e., the occurrence of DLT) and a new estimate of the MTD will be derived.

Enrollment into the next cohort will only resume after the Sponsor and the Investigators have jointly decided on the next dose-escalation step. Subject to clinical judgment, a new cohort of participants will be dosed at the new estimate of the MTD or the highest allowable dose based on pre-specified safety constraints as described below, whichever is lower and as guided by the mCRM-EWOC model. The design will continue as described, assigning participants to the MTD as estimated from all of the DLT data cumulatively, until one of the pre-defined stopping criteria is satisfied (see Section 4.1.4) or the pre-determined sample size of 60 DLT-evaluable participants is reached, whichever comes first. *Depending on emerging PK and safety data, the dose escalation may be evaluated taking into account sCEA levels at baseline in a sensitivity analysis (i.e. dose escalating more conservatively in the event toxicity is associated with low baseline sCEA levels).*

Built-in safety constraints are in place to prevent exposing participants to undue risk of toxicity, i.e., for Q3W dosing schedule, maximum allowable dose-increment, in absence of DLT, will be a maximum of 100%; if one DLT occurs then, an increment of 50% maximum will be allowed. The maximum dose that could be assessed in Part II will be 400 mg IV (see Section 4.3).

Provisional dose-levels in absence of DLT are listed in Table 9.

Table 9 Provisional Dose Levels in Absence of DLT

Dose Level	Dose (mg)	Dose-Increment if no DLT (%)	Next Dose if no DLT (mg)
1	1.6	100	3.2
2	3.2	97	6.3
3	6.3	90	12
4	12	67	20
5	20	100	40
6	40	100	80
7	80	88	150
8	150	100	300
9	300	33	400
10	400	N/A	N/A

Dose-frequency may be adjusted depending on the emerging PK data for RO7172508 and given an appropriate previously observed safety and tolerability profile. Different dosing schedules (e.g., non-fractionated and/or fractionated dosing) may be tested in parallel. If a decision is made to adjust the dosing schedule during the course of dose-escalation, the mCRM-EWOC algorithm will be updated with the available participant data and adapted to account for any difference in exposure of the new schedule. The initial starting-dose will not exceed a dose already tested and considered safe. Safety and DLT window may also be adapted. If fractionated dosing is implemented, the DLT window will be extended until the end of the cycle in which the planned full dose is administered.

- Dose-escalation to SC MTD

Once an MTD or OBD has been defined, or relevant clinical activity is seen (e.g., PR or better according to RECIST) for IV route of administration and schedule, SC administration will be tested. The starting dose *and regimen* for SC will be proposed based on the evaluation of the safety and efficacy data observed following IV administration; however, due to practical considerations, a minimum dose of 2 mg is defined for a single SC administration (Section 4.3).

In the *QW* cohorts, RO7172508 will be administered *three times per cycle (i.e.* QW*)*, with a maximum starting-dose of one third of the RO7172508 IV MTD dose or, in case MTD has not been reached, of the highest safe dose ≥ *6 mg* tested in the IV dose-escalation part. *For a Q3W regimen the starting dose will not exceed the highest safe dose tested in the IV Q3W dose escalation.*

The maximum allowed dose will be 160 mg QW *or 400 mg Q3W* (flat dose). Different dosing schedules (e.g., non-fractionated and/or fractionated dosing) may be tested.

For the SC administration, the mCRM-EWOC model will be updated to account for the available IV administration participant data and the difference in exposure with added uncertainty, given that the different routes of administration could lead to different safety profile. Each cohort will enroll a minimum of 3 participants. Enrollment and dose-escalation rules (i.e., stopping rules and maximum allowed increments) in Part II SC will be the same as the ones applied in Part II IV. DLT window will be the same as in Part II IV but may be updated based on emerging data. The dose-escalation will continue as described until one of the pre-defined stopping criteria is satisfied (see Section 4.1.4) or the pre-determined sample size of 60 DLT-evaluable participants is reached, whichever comes first.

No intra-participant dose-escalation will be allowed in Part II.

The OBD (IV and SC) will be selected based on the overall clinical safety and activity, as well as available PK and PD data for RO7172508. *Data will be listed and summarized by* dose group as described in the analysis section (see Section 9.4).

Once a schedule, route of administration and OBD has been selected, and in case efficacy is observed during dose-escalation, disease-specific expansions may be opened to confirm these efficacy signals. The protocol will be amended in this case to describe treatment of these cohorts. *If one route of administration is not unequivocally superior, and a decision cannot be taken during or at the end of dose escalation, both routes of administration may be compared in disease specific expansions. Criteria for selection of a route of administration will then be added via the protocol amendment preceding the expansions, including endpoints.*

4.1.3 Obinutuzumab Pre-treatment

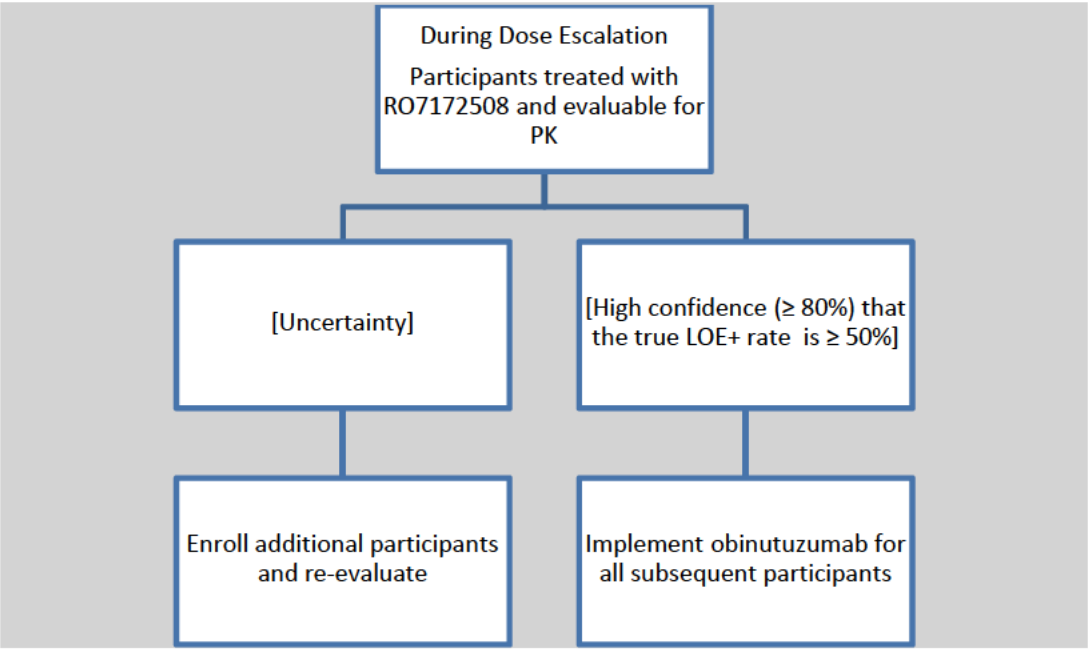
During the course of the study, the need for obinutuzumab pre-treatment will be assessed based on loss of RO7172508 exposure and/or ADA-related safety events. Previous experience with the combination of immunotherapy and obinutuzumab has shown the capacity of obinutuzumab to abrogate ADA formation, thereby maintaining exposure to the investigational compound as determined by PK analysis (see Section 2.2.2 and the RO7172508 investigator's brochure for further references).

During the course of the dose escalation, the decision to implement obinutuzumab will be based on a Bayesian posterior probability approach (see Appendix 8 for further details). At the time of the evaluation, if there is high confidence (80% confidence level) that the underlying true rate of participants with relevant loss of exposure is above 50% then obinutuzumab pre-treatment will be introduced for all subsequent participants in the study (see Section 6.1 and Appendix 8). If the criteria are not met, the dose escalation will proceed without obinutuzumab pre-treatment until the next assessment or the end of the dose escalation, whichever is reached first (see Appendix 8).

If obinutuzumab will be implemented during the course of the dose escalation, then the dose escalation will be run under the same condition as defined for Part II without obinutuzumab. The starting dose will be a dose that has been safely tolerated in Part II without obinutuzumab. Escalation, stopping rules and maximum number of participants applied to Part II will also apply to Part II with obinutuzumab pre-treatment.

The first assessment on the implementation of obinutuzumab will be conducted once PK data following 3 cycles of treatment are available from at least 14 participants across both Part I and II (see Appendix 8). Loss of exposure is defined as at least a 70% reduction in C_{max} at Cycle 3 from Cycle 1 in a participant. This threshold may be adapted based on emerging PK data. Ongoing assessments of safety and PK data will be performed for each cohort and at the end of dose escalation, to continuously evaluate the criteria for implementation of obinutuzumab pre-treatment. In addition, the incidence and titer of ADAs will be assessed on an ongoing basis throughout the study.

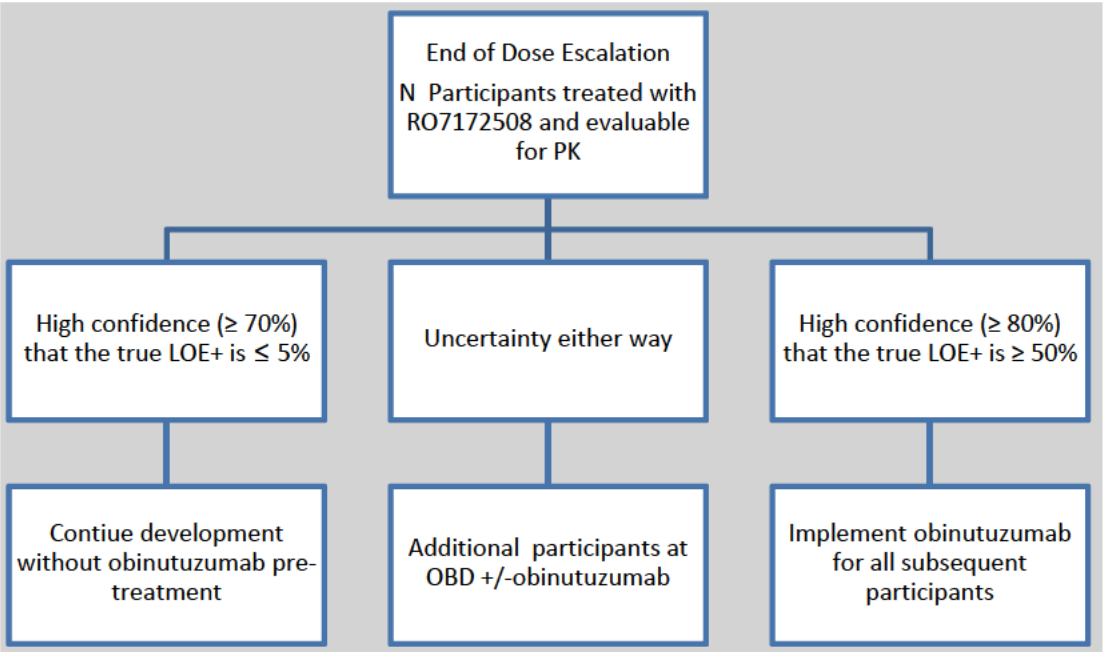
Figure 4 *Decision Tree During Dose Escalation*



If at the end of the dose escalation, the criteria to implement obinutuzumab pretreatment has not been met and at the same time, there is low confidence (i.e. <70% confidence level) that the true rate of loss of exposure is < 5%, then additional participants will be enrolled (see Appendix 8). Participants will then be randomized to cohorts at the OBD with or without obinutuzumab to further evaluate the safety and PK profile.

The need of obinutuzumab for further clinical development of RO7172508 will be determined based on the overall assessment of safety and PK data as well as pharmacodynamics effects.

Figure 5 *Decision Tree at End of Dose Escalation*



The total number of participants with relevant loss of exposure required to meet the criteria at subsequent evaluations, will depend on the actual number of participants enrolled and on the number of cohorts necessary to complete the dose escalation. For operating characteristics see Appendix 8.

Independent from loss of exposure, obinutuzumab pretreatment will be initiated if there is evidence of ADA-mediated hypersensitivity reactions or other safety signals that are likely related to ADAs. In such instance, obinutuzumab will be implemented for all subsequent participants and the enrollment of participants without obinutuzumab will be stopped.

4.1.3.1 Dose-Limiting Toxicities

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

- Hematological toxicities defined as:
  - Grade 4 neutropenia (i.e., absolute neutrophil count [ANC] $< 0.5 \times 10^9$ cells/L for a minimal duration of one week).
  - Grade 3 and 4 febrile neutropenia.
  - Grade 4 thrombocytopenia lasting > 48 hours
  - Grade 3 thrombocytopenia associated with bleeding episodes.

- Grade ≥ 3 non-hematological toxicity with the following exceptions:
  - Alopecia (any grade)
  - Grade 3 nausea or vomiting that resolves to Grade ≤ 1 with or without supportive therapy within one week.
  - Grade 3 hypophosphatemia and transient Grade 3 hyperbilirubinemia resolved within one week.
  - Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within one week.
  - Fever > 40°C (i.e., Grade 3) that occurs within 48 hours of RO7172508 infusion and improves to ≤ 40°C (Grade ≤ 2) within 48 hours and fully resolves within one week.
  - Grade 3 arthralgia that can be adequately managed with supportive care or that improves/resolves to Grade ≤ 2 within one week.
  - Grade 3 diarrhea, colitis, enteritis that resolves to Grade ≤ 1 within one week with no fever or dehydration.
  - Laboratory values of Grade ≥ 3 that are judged not clinically significant by the Investigator.
  - Grade 3 tumor pain that starts within 24 hours of infusion and improves/resolves to Grade ≤ 2 within one week.
  - Grade 3 hypoxia that starts within 24 hours of infusion and improves/resolves to Grade ≤ 2 within one week.
  - In participants with lung lesions, Grade 3 transient dyspnea secondary to localized lung edema that starts within 24 hours of infusion and resolves to Grade 1 or baseline within one week, and transient bronchospasm that resolves within 24 hours.
  - In participants with liver lesions, Grade 3 transient increase of bilirubin, transaminases (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) and/or gamma-glutamyl transferase (GGT) that starts within 24 hours of infusion and recovers to Grade 1 or baseline within one week.

Failure to recover from any RO7172508-related toxicity that results in a dose-delay of more than 14 days (any regimen) is defined as a DLT.

4.1.4 Stopping Rules Criteria

The dose-escalation will be halted if, for each route of administration or schedule, either:

- The MTD has been reached as determined by the model (Appendix 8) and at least 6 participants have been already dosed at the current estimate of the MTD (± 20%).
- The maximum of 60 DLT-evaluable participants is reached.

Due to the exploratory nature of this clinical study, any part of its conduct can be discontinued at any time at the discretion of the Sponsor. This will not constitute a

premature termination of the study. The Sponsor will notify the Investigators and Health Authorities if the study is discontinued or the development program is terminated.

4.1.5 Communication Strategy

The Investigators and the Sponsor will communicate regularly and on an ad-hoc basis to discuss the occurrence of any safety events including DLTs. At the end of each treatment cohort, the Sponsor will convene a joint teleconference with the participating Investigators. Dose-escalation decisions and selection of the dose for the next cohort of participants will be guided by the pre-defined escalation steps for Part I and mCRM-EWOC recommendation for Part II in addition to the review of all relevant available data including DLT information. Study Investigators and the Sponsor should reach a consensus on the next dose-level and may include de-escalation and/or expansion of recruitment into particular cohorts.

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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

The biomarker/PD assessments in this study are guided by the mode-of-action (MoA) and will focus on measuring CEA-expression (soluble in blood, and tumor by IHC) and immune cell activation in both tumor and blood (soluble and cellular assessments).

4.2.1 Rationale for Modified Continuous Reassessment Method of Escalation with Overdose Control

The Part II dose-escalation of this trial 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 (Rogatko et al 2007) and is one of the key elements of the Food and Drug Administration (FDA)'s Critical Path Initiative. Clinical judgment can always override the Bayesian adaptive design recommendations in the dose-selection process.

The primary objective of a dose-escalation trial, including the present trial, is to determine a MTD or recommended dose for Phase II. DLTs are the driver of dose-allocation and act as an important factor to define the MTD; however, DLTs are not equal to severe DLTs. DLTs traditionally are defined by the occurrence of severe toxicities during a relatively shorter period of time of systemic cancer therapy, which is called the DLT observation window.

The DLT observation window is usually the first treatment cycle of systemic cancer therapy in order for treated participants to have complete information on toxicities (DLTs)

prior to the next dose assignment in conventional dose-escalation designs. Toxicity induced by *cibisatamab* occurred predominantly within the first few days after the initial administration of the drug. Therefore, in line with this, a 3-week DLT window will be implemented in Part II of this study (or 6-week DLT window if a fractionated dosing schedule is implemented).

The mCRM-EWOC design has many favorable characteristics; first, it adaptively fits a DLT dose-response curve by incorporating toxicity data from eligible participants among different cohorts, and non-clinical or clinical information from compounds with similar MoA contributes by building an informative prior distribution of the statistical model. Second, it locates the MTD efficiently without pre-specifying dose-levels in each cohort. Dose-selections are made based on the DLT dose-response curve measured by a two-parameter logistic model over the dose-range, subject to clinical judgment and mandated safety constraints that limit the size of dose-increments. Moreover, the EWOC algorithm highly reduces risks of exposing participants to overly toxic doses.

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).

In addition, hypothetical dose-escalation runs using the design and simulations demonstrate the validity of the operating parameters of the design as implemented for this study (Appendix 8).

4.2.2 Rationale for Study Population

The study will be conducted in adult male and female participants with locally advanced and/or metastatic CEA-positive solid tumors who have progressed on SOC treatment, are intolerant to SOC, and/or are non-amenable to SOC.

Clinical and non-clinical studies have suggested that a wide array of tumors may respond to CEA-targeted TCBs. Therefore, this study will recruit participants with all types of advanced and/or metastatic solid tumors with cytoplasmic and/or membranous CEA expression in ≥20% of cells at intensities greater than at least IHC 1+ on archival material (or fresh biopsy when archival is not available) which are not amenable to SOC treatment. In the single participant cohort part of the study (Part I), participants require a high CEA expression (≥20% of cells at intensity 2+/3+) to ensure interpretability of safety parameters including potential tumor inflammation.

RO7172508 has the potential to bind to circulating sCEA, therefore, the exposure may be impacted following administration of low doses of RO7172508. A maximum baseline sCEA level has been indicated for doses < 12 mg to minimize the impact of RO7172508 binding to sCEA. *Preliminary PK data from the current study suggest sCEA may also impact the clearance of RO7172508. In order to further explore this relationship, at least 3 patients in each cohort in Part II should have a baseline sCEA level of ≤ 20 ng/mL.*

The maximum concentration of sCEA in a participant was calculated in order to observe at least 80% recovery of free RO7172508 at the predicted C_{max}. Assuming instantaneous equilibrium and a monovalent binding of RO7172508 to sCEA, one could express free-concentration of RO7172508 in plasma at time of administration as follows:

$$RO7172508_{free} = \frac{L_{tot} - R_{tot} - K_d - \Delta^{0.5}}{2}$$

$$\Delta = (L_{tot} + R_{tot} + K_d)^2 + 4 \times L_{tot} \times K_d$$

where L_{tot} is the total concentration of RO7172508, R_{tot} is the total concentration of sCEA, and K_d is the dissociation constant of the complex RO7172508-sCEA.

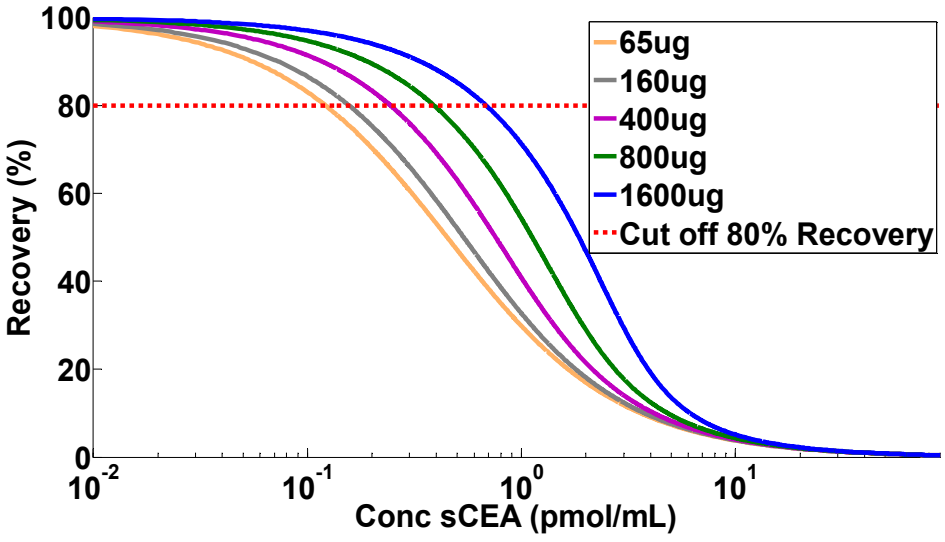
All calculations are performed assuming following parameter values:

- $K_d = 390\ pM$,
- $MW_{RO7172508} = 195000\ Da$,
- MW_{sCEA} = 180000-200000 *Da*,
- $V_c = 40\ mL.Kg^{-1}$
- $BW_{human} = 70\ Kg$

where MW stands for molecular weight, V_c stands for central volume of distribution and BW stands for body weight.

The recovery of RO7172508 at C_{max} was calculated using the above parameters for predicted doses < $12\ mg$ (Figure 6).

Figure 6 Recovery of RO7172508 in the Presence of sCEA



According to those simulations, sCEA concentration expected to produce 80% recovery for RO7172508 at C_{max} for the different clinical doses are presented in Table 10:

Table 10 sCEA Concentrations Predicted to Result in 80% Recovery of RO7172508 at Doses *Less Than 12 mg*

Dose (μg)	*65*	*160*	*400*	*800*	*1600*
sCEA concentration (ng/mL)	*22-24*	*28-31*	*44-49*	*70-78*	*123-137*
Dose *(mg)*	*3.2*	*6.4*	*12*	-	-
sCEA concentration (ng/mL)	*229-254*	*440-489*	*809-899*	-	-

4.2.3 Rationale for Control Group

Not applicable.

4.2.4 Rationale for Biomarker Assessments

RO7172508 was designed to target tumors that express CEA and to concomitantly engage immune cells leading to their activation and proliferation, which culminates in tumor lysis. Non-clinical studies have confirmed the expected MoA of RO7172508 by mediating tumor killing, induction of T-cell activation markers (CD25 and CD69), cytokine release (interferon (IFN)γ, tumor necrosis factor (TNF)α, granzyme B, interleukin (IL)-2, IL-6, and IL-10), and proliferation of T-cells. Furthermore, the MoA of RO7172508 occurs only if simultaneous binding (cross-linking) of T-cells to CEA-expressing tumor cells takes place. RO7172508 treatment may result in changes in peripheral blood immune cells and soluble circulating markers such as cytokines or tumor markers that are related to the MoA of RO7172508. Hence, plasma samples will be collected and analyzed for exploration of soluble factor changes (including but not limited to sCD25, IL-6, IFNγ, TNFα, etc) and tumor markers (including but not limited to sCEA, etc) that may be associated with treatment benefits or toxicities. Blood samples will also be collected and analyzed with respect to alterations in the number and activation/differentiation of immune cells (including but not limited to CD8+/HLA-DR/Ki67+, etc) as a consequence to treatment with RO7172508.

Tumor biopsy samples will only be collected from participants enrolled in Part II of the study. Mandatory tumor biopsies will be performed on two occasions: once during screening (pre-treatment) and once during treatment with RO7172508 on Cycle 2 Day 8), except for NSCLC patients where there is no accessible lesion. An optional biopsy may be taken at disease progression or long-lasting stable disease if the participant consents to this sample being taken. If preliminary data suggest that modification of the on-treatment tumor biopsy time-point would be more appropriate, alternative on-treatment tumor biopsy time-points may be considered in the future cohorts. The goals of these analyses will be (i) to establish a dose−response relationship and (ii) to understand the MoA of RO7172508 at the tumor site.

It is expected that upon treatment, the number and activation/differentiation status of intra-tumoral immune cells as well as their location will change. Such changes will be determined by flow cytometric and/or IHC methods and will be analyzed. Changes such as the density of different immune cell lineages (including but not limited to CD4+ T-cells, CD8+ T-cells, B-cells, natural killer (NK) cells, and macrophages) and their activation/differentiation status (including but not limited to CD25, Ki67, PD1, TIM3, etc) as well as TCR Vβ repertoire changes will be examined. The expression of tumor markers (including but not limited to PD-L1) will also be examined.

Administration of therapeutic antibodies can be associated with IRRs and cytokine release syndrome (CRS). Therefore, cytokines, including but not limited to IL-6, IFNγ, TNFα, and inflammation markers, will be assessed in serum or plasma samples during treatment and in the event of an IRR/CRS. Because these measurements also represent safety measures, they will be examined in participants enrolled in both Part I and Part II.

The specimens will be used for research purposes to identify biomarkers that are useful to predict and monitor response to RO7172508 treatment and safety, assess PD effects of RO7172508 treatment, and investigate the mechanism of resistance to therapy.

4.3 DOSE JUSTIFICATION

4.3.1 RO7172508

The entry-into-human starting flat dose of 65 μg was derived from incorporating an integrated approach, which was informed by in vitro activity in high-CEA expressing tumor cells as well as clinical safety experience with *cibisatamab* (see RO7172508 Investigator's Brochure). Compared to a classical minimum anticipated biological effect level (MABEL) approach, the approach used here reduces the number of participants exposed to sub-therapeutic doses of RO7172508 while ensuring that the starting-dose is in a safe range.

Taking into account 20-fold potency increase, a 400 μg dose of RO7172508 would be equivalent to 8 mg dose of *cibisatamab* (dose with no relevant cytokine increase documented and no Grade 3-related AEs reported).

Based on the available data, the Sponsor has defined the following intermediate doses in Part I:

- Second cohort: 160 μg
- Third cohort: 400 μg
- Fourth cohort: 800 μg
- Fifth and last cohort: 1.6 mg

Incremental dose-increases may be altered based on emerging PK, PD and safety data but will not exceed 3-fold. If there is no safety concern reported in Part I during the safety

observation period (stopping rule: any RO7172508-related event of Grade ≥ 2 toxicity reported within the DLT window), Part II of the study will start with a dose of 1.6 mg. Dose-escalation for Part II will follow the mCRM-EWOC design (see Section 4.1.2).

A maximum dose of 400 mg *Q3W* of RO7172508 has been defined. The C_{max} observed at Cycle 1 of 400 mg (MTD) *cibisatamab* was 113 μg/mL. Assuming a potency factor of 20, an equivalent RO7172508 C_{max} of 5.6 μg/mL is estimated to be achieved by 25 mg. The clinical potency may differ from the in vitro levels; therefore, a maximum dose of 400 mg has been defined to allow this to be tested. The dose-escalation will only take place once a full evaluation of safety data has taken place and the dose-increment levels may be reduced to ensure the participant's safety. Dose-fractionation may also be implemented in Cycle 1 where a dose not exceeding 400 mg will be administered over one cycle e.g., 40 mg on Day 1, 120 mg on Day 8 and 240 mg on Day 15. The maximum SC dose administered QW will be 160 mg QW which is 480 mg over a three-week period/*cycle*. By applying a conservative bioavailability of ~80% this would equate to 400 mg Q3W IV.

Further details are provided in the RO7172508 Investigator's Brochure.

4.3.2 Obinutuzumab

If required, during the course of this study, based on the incidence of ADA-induced loss of exposure or safety events, obinutuzumab will be administered as detailed in the SoA (Section 1.3). Obinutuzumab will be administered as pre-treatment for RO7172508 either as 2000 mg of obinutuzumab IV on one day (Day -7) or as 1000 mg of obinutuzumab IV on 2 consecutive days (Day -7 and Day -6) as specified in the SoA as per the site's choice. Details regarding the infusion process are provided in Section 6.1. ADA titers and PK of both RO7172508 and obinutuzumab will be monitored as described in Section 4.1.3.

The interval between obinutuzumab and the start of treatment has been determined based on Study BP39365, which is exploring the clinical activity of RO6874281 (FAP-IL2v) in combination with atezolizumab. Five patients were pretreated with obinutuzumab 7 days prior to the combination treatment. It could be confirmed that complete B cell depletion was observed at the start of the combination treatment seven days after obinutuzumab was administered. There was no evidence of ADA formation in these participants when assessing ADA titers for RO6874281 (FAP-IL2v) and atezolizumab (RO5541267) up to 32 weeks of treatment. One patient showed positive ADA titers after 32 weeks of RO6874281/atezolizumab combination, which correlated with the reconstitution of B cells. Another patient remains on study after 52 weeks with no evidence of ADA titers and B cells remain depleted. Without obinutuzumab pretreatment in Study BP39365, the incidence of ADAs is approximately 80%. The kinetics of B-cell depletion and repletion have also been studied in Study BO20999 and following the administration of obinutuzumab a rapid depletion of B-cells was observed by Study Day 8 in CLL patients (first measurement after administration).

Further details are provided in the obinutuzumab Investigator's Brochure.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study globally. Because of the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.2.

Participants in this study are patients who have locally advanced and/or metastatic tumors with cytoplasmic and/or membranous CEA expression in ≥20% of cells at intensities greater than at least IHC 1+.

In Part I, approximately 5 participants will be enrolled. In Part II, *up to* approximately *75* participants during each dose-escalation*, including additional 15 participants* (150 participants total in both IV and SC) will be enrolled (Section 9.2). *In case the OBD is evaluated with and without obinutuzumab, an additional 15 participants may be enrolled.*

Further participants may be treated in disease-specific expansions, once optimal schedule, route of administration and OBD have been determined.

Prospective approval of protocol deviations from recruitment and enrollment criteria, 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:

Informed Consent

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

Age

2. Age ≥ 18 years.

Type of Participants and Disease Characteristics

3. **For Part I** (single participant cohorts), participants with locally advanced and/or metastatic solid tumor with confirmed cytoplasmic and/or membranous high CEA expression in tumor tissue (≥ 20% of tumor cells staining with CEA IHC 2+ or 3+

intensity) is required (participants without archived tumor tissue available for testing must have a lesion amenable to biopsy). Participants must have progressed on a SOC therapy, be intolerant to SOC, and/or are non-amenable to SOC.

4. For < *12 mg d*ose cohorts, serum CEA (sCEA) levels below a certain threshold is required as follows:
    - For dose cohorts 65-159 μg, a*n* sCEA level of < 22 ng/mL.
    - For dose cohorts 160-399 μg, a*n* sCEA level of < 28 ng/mL.
    - For dose cohorts 400-799 μg, a*n* sCEA level of < 44 ng/mL.
    - For dose cohorts 800-1599 μg, a*n* sCEA level of < 70 ng/mL.
    - For the dose cohort of 1.6 - 3.1 mg, a*n* sCEA level of < 123 ng/mL.
    - *For the dose cohort of 3.2 - 6.3 mg, an sCEA level of <229 ng/mL.*
    - *For the dose cohort of 6.4 -11.9 mg, an sCEA level of <440 ng/mL.*

If dose fractionation is implemented, the sCEA threshold for inclusion should correspond to the dose range of the first dose administered.

For Part II, at least 3 participants in each cohort should have a baseline sCEA level ≤ 20 ng/mL.

5. For Part II, participants with locally advanced and/or metastatic solid tumor expressing cytoplasmic and/or membranous high-CEA or low-CEA on archival material (or fresh biopsy when archival is not available), who have progressed on a SOC therapy, are intolerant to SOC, and/or are non-amenable to SOC. Participants must have a lesion amenable to biopsy (except participants with NSCLC, which may be enrolled with archival tissue available only). *For participants with colorectal cancer (CRC) only, the CEA assessment by IHC should be performed but the result is not required to enroll the participant.*
    - High-CEA: ≥ 20% of tumor cells with IHC 2+ and/or 3+
    - *L*ow-CEA: *≥ 20% of tumor cells with the sum of any IHC intensity (1+, 2+ and 3+) and not considered CEA-High*
6. Radiologically measurable disease according to RECIST v1.1.
7. Life expectancy (in the opinion of the Investigator) of ≥ 12 weeks.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1.
9. All acute toxic effects of any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade ≤ 1 or returned to baseline except alopecia (any grade) and Grade 2 peripheral neuropathy.
10. Adequate hematological function: neutrophil count of ≥ 1.5 × 109 cells/L, platelet count of ≥ 100,000/μL, and hemoglobin ≥ 8 g/dL (4.9 mmol/L) including lymphocytes within normal limits (≥ 0.8 × 109 cells/L).
11. Adequate liver function: total bilirubin ≤ 1.5 × the upper limit of normal (ULN; excluding Gilbert's Syndrome), *aspartate aminotransferase* (AST) and/or *alanine aminotransferase* (ALT) ≤ 2.5 × ULN (in case of liver metastases, ≤ 5 × ULN).

12. Adequate renal function: creatinine clearance by Cockcroft Gault formula ≥ 60 mL/min for participants with, in the Investigator's judgment, serum creatinine levels that do not adequately reflect renal function.
13. Adequate lung function: vital capacity and forced expiratory volume in first second > 65% of age and body-weight predicted normal. Diffusion capacity > 55% of predicted normal.

Sex

14. Male and female participants

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

a) Female Participants

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Women of non-childbearing potential (WONCBP), as defined in Appendix 5.
- Women of childbearing potential (WOCBP), who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year from screening until 2 months after the last dose of RO7172508. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, and copper intrauterine devices (see Appendix 5).
  - Have a negative pregnancy test (blood) within one week prior to the first study treatment administration (applicable to premenopausal women and women ≤ 2 years after start of menopause (menopause is defined as amenorrhea for > 2 years).

b) Male Participants

During the treatment period and for at least 2 months after the last dose of study treatment, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom *or a* contraceptive method that result in a failure rate of < 1% per year, with partners who are WOCBP (as defined in Section 1 of Appendix 5).
- Refrain from donating sperm during the study.

5.2 EXCLUSION CRITERIA

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

Medical Conditions

1. Participants with a history or clinical evidence of central nervous system (CNS) primary tumors or metastases including leptomeningeal metastases unless they have been previously treated, are asymptomatic, and have had no requirement for steroids or enzyme-inducing anticonvulsants in the last 14 days before screening.
2. Participants with non-irradiated lesions > 2 cm at critical sites (e.g., paraspinal, paratracheal) where tumor swelling induced by RO7172508 is expected to lead to significant complications.
3. Participants with another invasive malignancy in the last 2 years (with the exception of basal cell carcinoma and tumors deemed by the Investigator to be of low likelihood for recurrence).
4. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or contraindicate the use of an investigational drug, including diabetes mellitus and history of relevant pulmonary disorders.

Diagnostic Assessments

5. Uncontrolled hypertension (systolic blood pressure [*S*BP] > 150 mmHg and/or diastolic BP *[DBP]* > 100 mmHg), unstable angina, congestive heart failure (New York Heart Association (NYHA) > 1, serious cardiac arrhythmia that requires treatment with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia, and history of myocardial infarction within 6 months of enrollment.
6. Active or uncontrolled infections.
7. Known hepatitis B or C (active replicating).
8. Major surgery or significant traumatic injury < 28 days prior to the first RO7172508 administration (excluding biopsies) or anticipation of the need for major surgery during study treatment.
9. Dementia or altered mental status that would prohibit informed consent.
10. Baseline corrected QT interval of > 470 ms. Participants with baseline resting bradycardia < 45 beats per minute (bpm) or baseline resting tachycardia > 100 bpm.
11. Radiotherapy within the last 28 days prior to the first RO7172508 administration with the exception of limited-field palliative radiotherapy.
12. Presence of <u>bilateral</u> lung lesions with either > 3 lesions per lung or ≥ 1 lesion per lung with a diameter > 3 cm *(only unequivocal lesions of > 1cm are to be counted for this criterion, unless there is miliary metastatic-type diffuse disease, then these participants are ineligible)*.

Prior/Concomitant Therapy

13. Concurrent therapy with any other investigational drug (defined as treatment for which there is currently no regulatory authority-approved indication) < 28 days prior to the first RO7172508 administration.
14. Last dose with an immunostimulating or immunosuppressive therapy (e.g., IFN-α, IFN-β, IL-2, etanercept, infliximab, tacrolimus, cyclosporine, or mycophenolic acid) < 28 days prior to the first RO7172508 administration.
15. Last dose of anti-CTLA4, anti-PD-L1, or anti-PD1 < 180 days prior to the first RO7172508 administration.
16. Expected need for regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease) within 28 days prior to the first RO7172508 administration.
17. Regular dose of corticosteroids within 28 days prior to Day 1 of this study or anticipated need for corticosteroids that exceeds prednisone 10 mg/day or equivalent within 28 days prior to the first RO7172508 administration. Inhaled and topical steroids are permitted.
18. Prior treatment with a bispecific T-cell engaging drug targeting CD3e and/or CEA.

Other Exclusions

19. Known hypersensitivity to any of the components of RO7172508.

Specific Exclusion Criteria if Pre-treatment with Obinutuzumab is Implemented

20. Known HIV (HIV testing will be performed at screening if required by local regulations)

21. Positive test results for chronic HBV infection (defined as positive HBsAg serology), HBcAb indicating an active viral infection and positive test results for HCV (HCV antibody serology testing).

22. Participants positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV ribonucleic acid (RNA).

23. History of progressive multifocal leukoencephalopathy.

24. Active TB requiring treatment within 3 years prior to baseline.

25. Latent TB diagnosed during Screening.

26. Positive test results for human T-lymphotropic virus 1 (HTLV 1)

27. HTLV testing is required in participants from endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia)

28. Known hypersensitivity to any of the components of obinutuzumab.

5.3 LIFESTYLE CONSIDERATIONS

There are no study-specific restrictions to meals and dietary requirements.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once providing they have not received the study drug and after discussion and agreement with the Sponsor. Re-screened participants should be assigned the same participant number as for the initial screening. Some essential procedures, such as biopsies, may be used from the initial screening period in agreement with the Sponsor. In the event that a fresh biopsy is taken during the screening period and the participant is not enrolled into the study, the formaldehyde-fixed paraffin-embedded (FFPE) biopsy block can be returned to the site upon site request.

5.5 RECRUITMENT PROCEDURES

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

6. TREATMENTS

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

The investigational medicinal products (IMP) required for completion of this study (RO7172508, *obinutuzumab* and tocilizumab) will be provided by the Sponsor. Administration of study treatment will be at the study centers under supervision of qualified site staff.

6.1 TREATMENTS ADMINISTERED

Table 11 summarizes the treatments administered.

Table 11 RO7172508 Summary of Treatments Administered

Study Treatment Name:	Part I RO7172508	Part II RO7172508
Dosage Formulation:	Solution for infusion and injection	Solution for infusion and injection
Unit Dose Strength(s)/Dosage Level(s):	20 mg/mL	20 mg/mL
Dose:	65 μg up to a maximum of 1.6 mg	1.6 mg up to a maximum of 400 mg IV 2 mg up to a maximum of 160 mg SC
Route of Administration:	IV	IV and SC
Dosing Instructions:	see Pharmacy Manual	see Pharmacy Manual
Packaging and Labeling:	Study treatment will be provided in a carton box (one labeled vial per box). Each carton box will be labeled as required per country requirement.	Study treatment will be provided in a carton box (one labeled vial per box). Each carton box will be labeled as required per country requirement.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

Please see the RO7172508 Investigator's Brochure and Pharmacy Manual for more details.

Administration of Obinutuzumab

The obinutuzumab Drug Product will be supplied by the Sponsor as a 50 mL single dose glass vial containing 1000-mg liquid concentrate in 40 mL (25 mg/mL) for infusion. In addition to the drug substance, the liquid is also composed of histidine/histidine-HCl, trehalose and poloxamer 188 (see Table 12).

Obinutuzumab will be administered either as a single dose of 2000 mg 7 days (D-7) before the first dose of RO7172508 (C1D1) or two doses of 1000 mg over days 6 and 7 days (D-6 and D-7) before the first dose of RO7172508 (C1D1).

For information on the formulation and handling of obinutuzumab, refer to the pharmacy manual and Obinutuzumab Investigator's Brochure.

Table 12 Obinutuzumab Summary of Treatment Administered

Study Treatment Name	***Obinutuzumab***
Dosage Formulation	*Concentrate for solution for IV infusion*
Unit Dose Strength(s)/Dosage Level(s)	*25 mg/mL*
Dose	*2000 mg or split doses of 2x 1000 mg*
Route of Administration	*IV*
Dosing Instructions	*see Pharmacy Manual*
Packaging and Labeling	*Study treatment will be provided in a carton (one labeled vial per box). Each carton will be labeled as required per country requirement.*

Administration of Tocilizumab

Administration of tocilizumab is based on clinical presentation of CRS and should follow the guidelines stated in Section 8.3.8.1.

Please see the tocilizumab Investigator's Brochure and Pharmacy Manual for more details.

Table 13 Tocilizumab Summary of Treatment Administered

Study Treatment Name:	Tocilizumab
Dosage Formulation:	Concentrate for solution for IV infusion
Unit Dose Strength(s)/Dosage Level(s):	200 mg/10 mL
Dose:	8 mg/kg IV
Route of Administration:	IV
Dosing Instructions:	see Pharmacy Manual
Packaging and Labeling:	Study treatment will be provided in a carton box (one labeled vial per box). Each carton box will be labeled as required per country requirement.

6.1.1 Pre-medication

All pre-medications should be captured as concomitant medications in the participant's electronic Case Report Form (eCRF). If during dose-escalation Grade ≥ 2 IRRs/CRS or tumor inflammatory events occur in the majority of participants, the utility of prophylactic pre-medication with systemic corticosteroids in preventing such events may be tested using the regimen as outlined in Table 14 (flat dosing) and Table 15 (for fractionated dosing). If successful, this regimen will then be used in future cohorts.

In the event that the change in the route of administration from IV to SC does not mitigate the tumor inflammatory events or IRRs, then the same steroid regimen may be implemented as described in Table 14 and Table 15. These regimens are based on the expected duration of inflammatory events and they may be reduced or modified based on emerging data. *Also, they may be extended from Cycle 1 to subsequent cycles, in case tumor inflammation and/or IRR occur at later cycles.* Pre-medication may also include 1000 ml saline, 50 mg indomethacin (or equivalent non-steroidal anti-inflammatory [NSAID]), and 50 mg diphenhydramine (or equivalent H1 antagonist).

Table 14 Steroid Use on Cycle 1 of RO7172508 Infusion to be implemented in the event of frequent IRR/CRS *or gastrointestinal RO7172508-related toxicity* occurrence after first administration

Timing	Dose
C1D1: 4 to 6 hours before RO7172508 infusion	*1* mg/kg *methylprednisolone* IV* 1 g paracetamol PO TID 2 mg loperamide PO
C1D1: approximately 2 hours after RO7172508 infusion	*1 mg/kg methylprednisolone IV**
C1D2: approximately 24 hours post-RO7172508 EOI	*1* mg/kg prednisone IV/PO* 1 g paracetamol PO TID 2 mg loperamide PO**
C1D3: approximately 48 hours post-RO7172508 EOI	0.5 mg/kg prednisone IV/PO* 1 g paracetamol PO TID
C1D4: approximately 72 hours post-RO7172508 EOI	0.5 mg/kg prednisone IV/PO* 1 g paracetamol PO TID

C: Cycle; D: Day; EOI: end of infusion; IV: intravenous; PO: oral; TID: 3 times a day.

** rounded up to next multiple of 10 mg (or equivalent doses of mid acting steroids)*

*** subsequent treatment with loperamide only to be given as clinically indicated*

Table 15 Steroid Use on Cycle 1 of RO7172508 *or gastrointestinal RO7172508-related toxicity* to be implemented in the event of frequent IRR/CRS persisting despite dose fractionation

Timing	Dose
C1D1: *4 to 6 hours* before RO7172508 infusion	*1* mg/kg *methylprednisolone* IV* 1 g paracetamol PO TID 2 mg loperamide PO
C1D1: approximately 2 hours post-RO7172508 EOI	*1* mg/kg prednisone IV/PO 1 g paracetamol PO TID
C1D*2*: *approximately* 24 hours *post*-RO7172508 *EOI*	*1* mg/kg prednisone IV/PO
C1D8: 60 minutes before RO7172508 infusion	*1* mg/kg *methylprednisolone* IV* 1 g paracetamol PO TID 2 mg loperamide PO**
C1D*8*: *approximately 2 hours post-RO7172508 EOI*	0.5 mg/kg prednisone IV/PO 1 g paracetamol PO TID
C1D*9*: *approximately* 24 hours *post*-RO7172508 *EOI*	0.5 mg/kg prednisone IV/PO
C1D15: 60 minutes before RO7172508 infusion	*1* mg/kg *methylprednisolone* IV* 1 g paracetamol PO TID 2 mg loperamide PO **
C1D1*5*: *approximately 2 hours* post-RO7172508 EOI	*1* mg/kg prednisone IV/PO 1 g paracetamol PO TID
C1D16: approximately 24 hours post-RO7172508 EOI	*0.5 mg/kg prednisone IV/PO*

C: Cycle; D: Day; EOI: end of infusion; IV: intravenous; PO: oral; TID: 3 times a day.

** rounded up to next multiple of 10 mg (or equivalent doses of mid acting steroids)*

*** subsequent treatment with loperamide only to be given as clinically indicated*

In addition to the above mentioned premedication regimens, additional premedication may be implemented after agreement between Sponsor and Investigators for prophylaxis of RO7172508-related toxicity at cycle 1 and/or at subsequent cycles:

- *From 30 to 60 minutes before administration of RO7172508, 5-HT3-receptor antagonist administration (preferably a long acting antagonist such as palonosetron 500 μg);*
- *Budesonide 9mg daily to start 3 days before first RO7172508 and to be continued up to 7 days after first RO7172508 administration.*

Subsequent RO7172508 Infusions

Participants who experienced a Grade 2 IRR *or other RO7172508-related toxicity within 24 hours of RO7172508 administration* on a previous infusion, should be pre-medicated for subsequent infusions. *The regimen indicated in Table 14 will be recommended for subsequent cycles, however in lieu of IV methylprednisolone administration, an equal oral dose of methylprednisolone (or equivalent) can be used. Similarly, the additional premedication regimens may be moved to subsequent cycles to prevent recurrence of the toxicity that occurred in Cycle 1. Premedication regimens for subsequent cycles may be reduced or omitted in case of ≤ Grade 1 events in the previous cycle.*

For participants who experience an IRR-like reaction with a single and isolated symptom, such as fever that occurs within 24 hours after the study treatment infusion was completed, the use of pre-medication such as paracetamol, anti-histamine, and corticosteroids is not foreseen prior to subsequent RO7172508 administrations. The event will be reported as a single AE (e.g., fever). Pre-medication with corticosteroids of those participants at subsequent infusions needs approval from the Sponsor and the treatment and management at the time of an event is at the discretion of the Investigator. Pre-medication may be changed based on emerging data *and the regimens described above should be considered as the maximum suggested regimens. After collecting information on the effectiveness of the above mentioned premedication regimens scheduling and dose intensities may be reduced but not increased.*

Premedication Prior to Obinutuzumab Administration

The use of corticosteroids, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and/or antihistamines is required to minimize expected IRR reactions associated with the administration of obinutuzumab. Pre-medication must be administered prior to obinutuzumab administration. A list of the mandatory pre-medications is provided in Table 16.

Hypotension may occur as a result of an IRR adverse event. Therefore, it is recommended that antihypertensive drugs not be given on the morning of, and throughout the infusion of obinutuzumab, even if clinically indicated. Patients with a history of cardiac disease should be monitored closely.

Table 16 Premedication Requirements for Obinutuzumab

Pre-Medication	*Timing of Administration*
Prednisolone 100 mg administered by IV infusion (or equivalent)	*At least 60 minutes prior to the obinutuzumab infusion*
Analgesic/anti-pyretic (e.g., paracetamol/oral acetaminophen 500 –1000 mg) administered orally or by IV infusion	*At least 30 minutes prior to the obinutuzumab infusion*
Antihistamine (e.g., oral diphenhydramine 50 –100 mg) administered orally or by IV infusion (or an alternative anti-histamine at an adequate dose)	*At least 60 minutes prior to the obinutuzumab infusion*

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

The packaging and labeling of the study medication will be in accordance with the Sponsor's standard and local regulations.

The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

Upon arrival of the IMPs at the site, site personnel will complete the following:

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

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the defined dose-level.

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

This is an open-label, non-randomized study. Participants who fulfill all of the inclusion criteria and none of the exclusion criteria are eligible to participate in the study and will be assigned to a treatment group/dose in consultation with the Sponsor. For Part I and Part II of the study, the assigned dose will be documented in the Confirmation of Enrollment and a participant number will be assigned. A participant Enrollment and Identification Code List must also be maintained by the Investigator.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the defined dose-level and the instructions given in the Pharmacy Manual. This individual will write the date dispensed and participant number on the study treatment box label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study.

6.5 CONCOMITANT THERAPY

6.5.1 Permitted Therapy

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant during screening until the follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency). The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF. All therapy and/or medication administered to manage adverse events should be recorded on the AE eCRF.

6.5.1.1 Radiotherapy

The use of palliative radiotherapy is allowed at any time during the study, **except for:**

- On days when RO7172508 is administered.
- During DLT evaluation period.
  - If radiotherapy is administered during the DLT evaluation period, the participant will not be evaluable.

Participants should not receive study treatment during radiation treatment.

6.5.2 Prohibited Therapy

All medications (prescription and OTC) taken within 30 days of study screening will be recorded on the appropriate eCRF. As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

The use of the following therapies is prohibited for at least 28 days prior to initiation of study treatment and during the study, unless otherwise specified below:

- Investigational or unlicensed/unapproved agents
- Immunotherapy/radio-immunotherapy
- Chemotherapy/targeted therapy
- Radiotherapy (with the exception of limited–field palliative radiotherapy; see Section 6.5.1.1).
- Biologic agents (e.g., bevacizumab, erlotinib).
- Chronic use of steroids (inhaled and topical steroids are permitted).
- Administration of a live, attenuated vaccine within 28 days before Cycle 1 Day 1 or anticipation that such a live attenuated vaccine will be required during the study.

6.6 DOSAGE MODIFICATION

In the event a dose-reduction is necessary, any subsequent study treatment will be administered after agreement with the Sponsor.

Should a participant experience a DLT in the first or in subsequent cycles or experience a toxicity of the same nature at the same or higher grade following re-exposure to RO7172508, the Investigator, after discussion with the Sponsor, will have the option to reduce the dose of RO7172508, if deemed clinically beneficial.

A delay of RO7172508 administration for up to two cycles independent of the schedule, will be acceptable to allow for resolution of toxicity to NCI CTCAE Grade $\leq$ 2 for hematological toxicities or Grade $\leq$ 1 for non-hematological toxicities (with the exception of a toxicity considered as non-RO7172508-related).

If the toxicity does not resolve to NCI CTCAE Grade ≤ 2 for hematological toxicities or ≤ 1 for non-hematological toxicities and the participant is unable to resume treatment with RO7172508 after this time (omission of two doses), no additional doses will be administered and the participant will be withdrawn from study treatment, unless the participant exhibits a clinical benefit and this is agreed by the Investigator and the Medical Monitor. It should be noted that infusions/cycles not occurring at the anticipated schedule, are considered as delayed, not missed.

Further dose-reductions may be implemented once safety and toxicity data from the dose-escalation have been evaluated.

If a participant experiences obinutuzumab-related toxicity on Day -7 that requires the subsequent administration of obinutuzumab on Day -6 to be delayed, administration of obinutuzumab up to Day -5 is acceptable. Any obinutuzumab-related toxicity should resolve to NCI CTCAE Grade ≤ 2 for hematological toxicities or ≤ 1 for non-hematological toxicities before RO7172508 administration. The first RO7172508 administration can be delayed for of up to 1 week and if toxicity persists, the start of RO7172508 treatment will need to be agreed with the Medical Monitor.

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer post-trial access to the study treatment (RO7172508) free of charge to eligible participants in accordance with the Sponsor's Global Policy on Continued Access to Investigational Medicinal Product.

A participant will be eligible to receive study treatment after the end of the study if all of the following conditions are met:

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

A participant will not be eligible to receive study treatment after the end of the study if any of the following conditions are met:

- The study treatment is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or would not otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the study treatment or data suggest that the study treatment is not effective for cancer.
- The Sponsor has reasonable safety concerns regarding the study treatment as treatment for cancer.

- Provision of study treatment is not permitted under the laws and regulations of the participant's country.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study-specific procedures as outlined in this protocol.

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

7.1 DISCONTINUATION OF STUDY TREATMENT

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

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

- Pregnancy
- Grade 3 IRR/CRS for RO7172508
- IgE-mediated hypersensitivity reactions, including anaphylaxis.
- Any toxicity which is not manageable with dose-delays (as allowed per protocol), dose-decrease and/or appropriate treatment.
- Symptomatic disease progression when there is a consensus that the participant will not benefit from study treatment.
- If a patient develops alanine aminotransferase or aspartate aminotransferase increase $>$ 10x ULN associated with the 3rd infusion of RO7172508 or later.

Participants who discontinue study treatment prematurely will be asked to return to the clinic for an End-of-Treatment visit (see Section 8.10.3) and may undergo follow-up assessments (see Section 8.10.4). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely may be replaced for the following reasons to ensure adequate numbers of evaluable participants:

- Participant who withdraws from the study prior to the treatment start may be replaced.
- Participants who fail to complete their DLT assessment period because of non-drug–related reasons.
- In the case of a major protocol violation when participants are excluded from Cycle 1 of treatment (these participants will be excluded from the MTD/DLT analysis

but might continue the treatment if deemed beneficial and according to clinical judgment).

- Cohorts may be expanded to acquire additional paired tumor biopsies.

Participants will be treated for 24 months (the treatment period may be modified if supported by emerging data) or until disease progression, loss of clinical benefit, unacceptable toxicities, or withdrawal from treatment for other reasons or death.

As with other immunotherapies, treatment beyond RECIST (Appendix 6) progression could be considered. The criteria below will be needed to continue treatment beyond initial apparent progressive disease per RECIST v1.1 (e.g., radiological progression secondary to tumor inflammation):

- Absence of clinical deterioration and Investigator–assessed potential clinical benefit for the participant and
- The participant is tolerating study treatment.

7.1.1 Temporary Interruption

If an IRR/CRS develops, the infusion of RO7172508 should be slowed down or interrupted. The participant should be monitored until complete resolution of the symptoms and treated as clinically indicated. Treatment or concomitant medication may include acetaminophen/paracetamol, antihistamine, IV saline, oxygen, bronchodilators, corticosteroids, and vasopressors, depending on the symptoms (see Section 8.3.8.1. Study treatment should be re-started as soon as medically justified in the opinion of the Investigator.

The infusion may be resumed at $\leq$ 50% (Grade 1 IRR/CRS) or $\leq$ 25% (Grade 2 IRR/CRS) of the previous rate. The infusion can be re-escalated to the initial rate if study treatment is considered well-tolerated after one hour of infusion.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

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

Participants who withdraw from the study for safety reasons will not be replaced. Participants who withdraw from the study for other reasons may be replaced only as described in Section 7.1.

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

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

7.3 LOST TO FOLLOW-UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant’s medical record.
- Should the participant continue to be unreachable, he/she will be considered to be lost to follow-up.

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

Based on continuous analysis of the data in this study, any sample type or biomarker evaluation not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Tumor assessments will be performed at the time-points defined in the SoA (Section 1.3). Tumor response will be evaluated according to RECIST v1.1 (Appendix 6) using unidimensional measurement such as CT scan or magnetic resonance imaging (MRI). Assessment of CT/MRI scans as tumor assessments will be performed at the sites during the whole study.

The data collected for RECIST v1.1 *(Appendix 6)*will be used by the Sponsor to calculate programmatically 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 cancer immunotherapy field (Seymour et al 2017).

Tumor assessment will be performed according to the SoA until disease progression or death. All tumor assessments after baseline may be done within one week of the scheduled visit.

Confirmation of PRs and complete responses (CRs) will be done at the next scheduled visit after at least 28 days from the initial response.

The criteria are needed for continuing treatment beyond RECIST v1.1-defined progression as defined in Section 7.1.

Submission of the latest pre-study or historical CT scans is required for assessment of tumor kinetic modelling within 12 weeks of participant entering the study if available.

8.1.1.1 Radiographic Assessments

Diagnostic CT scans should be acquired according to the guidelines in Appendix 6. At the Investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

MRI or positron emission tomography (PET)/CT (without contrast) scans may be used instead of CT scans in participants for whom CT scans are contraindicated, provided they permit consistent and precise measurement of target lesions during the study treatment period.

The same radiographic assessment modality and acquisition protocol should be used for all response evaluations, in order to ensure consistency across different time-points. A full radiographic assessment must be performed any time disease progression or if a relapse is suspected.

8.2 SAFETY ASSESSMENTS

Planned time-points for all safety assessments are provided in the SoA (Section 1.3). *In order to better understand related adverse events, if any unscheduled assessments are performed during the study as part of standard of care, such as biopsies at the time of inflammation, these samples and/or results can be shared with the Sponsor for further analysis.*

8.2.1 Physical Examinations

A physical examination will be performed by trained medical personnel at the study center at the visits indicated in the SoA (see Section 1.3). Physical examination will include body weight (at screening, during treatment, at the final or early termination visit, and at the safety follow-up visit) and height (at screening).

The physical examination should cover head and neck including lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems, and others, as applicable.

Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

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

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

8.2.2 Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed as outlined in the SoA (see Section 1.3).

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 will be taken before blood collection for laboratory tests but after electrocardiogram (ECG) collection when scheduled at the same time-point. At the discretion of the Investigator, measurements can be repeated if the values are abnormal or borderline.

Not every vital sign abnormality qualifies as an AE. Criteria for vital sign results that should be reported as an AE are listed in Appendix 3, Section 5.

8.2.3 Electrocardiograms

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

In case of abnormalities or clinical symptoms, unscheduled ECG assessments should be performed in triplicate. At each time-point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession. To minimize variability, it is important that participants be in a resting position for at least 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 should be performed prior to meals and any scheduled vital sign measurements and blood draws. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS complex, and PR and QT intervals, will be recorded on the eCRF. QTc using Bazett's correction factor (QTcB), QTc using Fridericia's correction factor (QTcF) and RR interval will be calculated by the Sponsor. Changes in T‑wave and U‑wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

8.2.4 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 separate Laboratory Manual and the SoA (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF if it fulfills the criteria defined in Appendix 2. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- 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 of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

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 is considered uncertain, screening laboratory tests may be repeated before randomization to confirm eligibility.

8.2.5 Medical History and Demographic Data

Medical history includes clinically significant diseases, demographic data (including age, sex, and self-reported race/ethnicity), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the AE 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 AE eCRF as follows:

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

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment.

Post-study adverse events and serious adverse events: 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 prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

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

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

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

During the study period, resolution of AEs (with dates) should be documented on the AE 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 AE eCRF.

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

8.3.3.2 Sponsor Follow-Up

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

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

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

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the 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 IEC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

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

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 2 months after the last dose of study treatment.

Male participants will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 2 months after the last dose of study treatment.

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

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

8.3.6 Non-Serious Adverse Events of Special Interest

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

NSAESIs of special interest for this study include the following:

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

  Transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

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

No disease-related events are expected for this study.

8.3.8 Management of Specific Adverse Events

Guidelines for the management of participants who experience specific AEs to the IMPs other than RO7172508 (obinutuzumab and tocilizumab) are provided in the obinutuzumab and tocilizumab Investigator's Brochure and local prescribing information. Guidelines for the management of participants who experience AEs associated with RO7172508 are provided in Table 17, Table 18, and Table 19. For cases in which management guidelines are not covered in this protocol or in the obinutuzumab/tocilizumab Investigator's Brochure and local prescribing information, toxicities should be treated as deemed appropriate by the Investigator according to best medical judgment and local medical guidelines. Please see the RO7172508 Investigator's Brochure for *further* details *of the safety profile.*

8.3.8.1 Infusion-Related Reactions/Cytokine Release Syndrome

Administration of RO7172508 may cause a spectrum of infusion-related adverse events that typically occur during, shortly after, or within 24 hours after the infusion and could be associated with an IRR or CRS.

IRRs are typically seen with the first two cycles and without symptoms of hypoxia and/or hypotension. In contrast, CRS is more likely to occur with the symptoms of hypoxia and/or hypotension at any cycle and with any symptom following from the third cycle onward. IRR events are therefore defined as taking place in association with the first two infusions and without symptoms of hypotension and/or hypoxia.

Given the overlap in signs and symptoms, IRRs may be indistinguishable from CRS, defined as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, shortness of breath, and renal, coagulation, hepatic, and neurologic disorders (Lee et al. 2014). Severe CRS may be associated with other clinical sequelae, such as disseminated intravascular coagulation and capillary leak syndrome.

Given that IRRs may be indistinguishable from CRS based on symptomatology, single-treatment management guidelines are being recommended for both IRRs and CRS, during or up to 24 hours after infusion of RO7172508. The approach to have single-treatment management guidelines for IRR and CRS will continue to be reviewed as additional safety data accumulate.

Table 17 provides guidelines for management of infusion-related reactions/ cytokine release syndrome.

Table 17 Recommendations for Management of IRRs and CRS considered related to RO7172508[a]

Symptoms	Guidance
Grade 1 Fever, constitutional symptoms	– If RO7172508 infusion is ongoing, slow infusion to ≤50% or interrupt infusion – Symptomatic treatment and supportive care – *Monitor fluid balance and administer IV fluids as clinically indicated* – At next cycle administer pre-medications that may include antihistamine, antipyretics/NSAIDS, antiemetic, and corticosteroids (See Table 14 *and* Table 15)
Grade 2 Hypotension: responds to fluids OR Hypoxia*: requires <40% FiO_2 (or ≤5 L/min of 100% O2) to maintain adequate hemoglobin oxygen saturation	– Follow all Grade 1 recommendations – Hold further RO7172508 treatment until symptoms completely resolved – *At the restart of the infusion, s*low down the rate of infusion to 25% of original rate – If event occurred during infusion, and symptoms recur with the same or greater severity following interruption of RO7172508 infusion, the infusion must be stopped immediately. *Consider to manage as a Grade 3 event.* No further RO7172508 will be administered for the cycl*e* – Monitor cardiac and other organ functions closely – Hemodynamic support as indicated and oxygen for hypoxia – Admit to ICU as appropriate – *Consider administering a single dose of tocilizumab IV 8 mg/kg* – If no improvement within 24 hours: **a)** Notify Medical Monitor **b)** Administer IV corticosteroids (e.g., methylprednisolone [2 mg/kg/day] or dexamethasone 10 mg if neurologic symptoms are present) – Additional monitoring and evaluation: – Consider 24 hour hospitalization – Work up for organ functions (e.g. liver, cardiac) based on clinical assessment of the Investigator – May receive RO7172508 in next cycle if symptoms resolve to Grade ≤1 with the approval of the Medical Monitor including considerations for dose reduction and/or reduction of infusion rate at the next administration. – At next cycle administer pre-medications that may include antihistamine, antipyretics/NSAIDS, antiemetic, and corticosteroids

Table 17 Recommendations for Management of IRRs and CRS considered related to RO7172508 [a] (cont.)

Grade 3 Hypotension: requires vasopressor support OR Hypoxia*: requires >40 % FiO_2 or >5 L/min O2 to maintain adequate hemoglobin oxygen saturation	– If RO7172508 infusion is ongoing, stop infusion immediately – No further RO7172508 will be administered for the cycle – Cardiopulmonary and organ function monitoring in ICU – Closely monitor and maintain fluid balance; and other supportive care as clinically indicated – Vasopressor support for hypotension with high and repeated doses if required – Notify Medical Monitor – Initiate IV corticosteroids (e.g., methylprednisolone [2 mg/kg/day] or dexamethasone 10 mg if neurologic symptoms are present) – Administer tocilizumab 8 mg/kg IV – If no clinical improvement within 24 h: repeat dose of tocilizumab 8 mg/kg – Additional monitoring and evaluation: – Hospitalize patient for 24 hours – Work up for organ functions (e.g. liver, cardiac) based on clinical assessment of the Investigator – Permanently discontinue RO7172508 *and follow the Schedule of Assessments* (Table 5)
Grade 4 Hypoxia: Mechanical ventilation required	– Follow all Grade 3 guidelines – Permanently discontinue RO7172508

[a] Grading of events is based on CTCAE V5.0

* Isolated hypoxia (without hemodynamic instability) requiring oxygen support in a patient with tumor (primary or metastatic) in the lung should be managed as per tumor inflammation guidelines (Table 18) and not per CRS guidelines (Table 17).

8.3.8.2 Suspected Tumor Inflammation

Adverse events associated with tumor inflammation have been reported with T-cell engaging therapies and are consistent with the mechanism of action of such therapies that lead to influx of T-cells into tumor sites. Tumor inflammation is driven by influx of T cells and it is dependent on the mechanism of action of RO7172508. Along with the volume increase dependent on the influx of T cells, there may be an additional volumetric component possibly dependent by local inflammation. Events involving tumor inflammation, including tumor flare, have been reported in studies with in-class agent cibisatamab. These events tend to occur with a short time to onset following administration and may present with varying degrees of severity.

In addition, depending on tumor size and anatomic location, events associated with tumor inflammation may potentially result in mass effects on vital structures, including airways, major blood vessels, and/or major organs. Depending on the nature of the tumor inflammation, further medical and/or surgical management may be necessary (e.g. anti-inflammatory agents, airway management, decompression, cardiac function monitoring in terms of ejection fraction). Participants with tumors involving critical anatomic locations should be closely monitored for tumor inflammation and prospective consideration for preventive or interventional measures may need to be considered or planned prior to dosing. The treating physician/study investigator should contact the Medical Monitor to discuss risk assessment and mitigation strategies prior to initiating RO7172508 treatment in case participants present disease closed to vital structures.

For further safety information, refer to the RO7172508 Investigator Brochure.

Table 18 provides guidelines for management of suspected tumor inflammation.

If corticosteroids are administered, taper before stopping treatment. In case of concurrent respiratory and other organ toxicities, follow the management recommendations for respiratory toxicities.

Table 18 Management of Suspected Tumor Inflammation

Event	Initial Management Recommendation	Action to be Taken with RO7172508
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 Grade4	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.

Table 18 Management of Suspected Tumor Inflammation (cont.)

Toxicities in other organs systems		
Grade 1 or 2	Monitor participant closely	Continue if Grade 1 event (for Grade 2 events, 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 permanent discontinuation (including liver enzyme elevations). Exceptions may be warranted after discussion of benefit/risk profile of a specific patient 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.	

8.3.8.3 Management of Diarrhea/Colitis

Table 19 provides guidelines for management of suspected diarrhea.

Patients should be closely monitored (including monitoring of renal function) and should be hydrated if clinically indicated to prevent renal insufficiency due to fluid depletion.

For Grade ≥ 2 diarrhea associated with the 3rd administration of RO7172508 or later, patient referral to a GI Specialist is recommended (including a colonoscopy and/or biopsy based on specialist input).

Table 19 Management of Diarrhea/*C*olitis

Event	Management Recommendations
Grade 1	• Continue treatment with RO7172508. • Initiate anti-diarrheal treatment (e.g., loperamide) as soon as possible. • Monitor the participant closely. • Ensure appropriate fluid intake. • If symptoms persist despite optimal anti-diarrheal treatment for more than 5 days, perform gastrointestinal (GI) work up*.
Grade 2	• Withhold treatment with RO7172508. • Initiate anti-diarrheal treatment (e.g., loperamide) as soon as possible • Monitor the participant closely, perform GI work up*. • Ensure appropriate fluid intake • If symptoms do not improve to Grade ≤1 despite optimal anti-diarrheal treatment within 2 days, consider treatment with IV or oral corticosteroids (1mg/kg/day oral prednisolone or equivalent). • If diarrhea does not improve after 48 hours of corticosteroid treatment of 1mg/kg/day, increase dose to 2mg/kg/day. • If symptoms do not resolve despite corticosteroid treatment, consider referring the participant to GI specialist • RO7172508 can be re-started if symptoms resolve to Grade ≤ 1.
Grade 3	a. Withhold treatment with RO7172508. b. Refer the participant to GI specialist for diagnostic procedures (stool culture, endoscopy) and appropriate treatment. • Initiate corticosteroid treatment IV (2mg/kg/day IV methylprednisolone or equivalent). • Ensure appropriate fluid intake. • RO7172508 can be re-started if symptoms resolve to Grade ≤ 1. • *If no improvement after 24 hours, consider treatment as per Grade 4 guidelines*
Grade 4	• Permanently discontinue treatment with RO7172508. • Refer the participant to GI specialist for diagnostic procedures (stool culture, endoscopy) and appropriate treatment. • Manage all symptoms by aggressive symptomatic treatment. • Initiate corticosteroid treatment IV. • If the there is no improvement for more than 48 hours, immunosuppressive treatment might be considered (such as infliximab).

* GI work up *for further evaluation (e.g. endoscopy) and* includes stool culture

8.3.8.4 *Management of Immunogenicity*

Administration of therapeutic antibodies may cause the formation of ADAs and immunogenicity is a potential risk for RO7172508. Severe AEs (including two fatal events) associated with ADA formation were observed during clinical development of in class agent cibisatamab.

All participants will be monitored at regular intervals for the development of ADAs against RO7172508 (see Section 8.5.1 for details). In case of emergence of AEs (in particular hypersensitivity reactions and CRS) possibly related to the development of ADAs against RO7172508, management will follow guidelines as summarized in Table 17. In all cases of AEs suspected to be associated with the development of ADAs, treatment discontinuation should be immediately considered even if the event is low grade after discussion with Medical Monitor.

As an additional mitigation strategy, obinutuzumab pre-treatment will be initiated if there is evidence of ADA mediated hypersensitivity reactions or other safety signals that are likely related to ADAs (see Section 4.1.3 for details). In such instance, obinutuzumab will be implemented for all subsequent participants and the enrollment of participants without obinutuzumab will be stopped.

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (see Appendix 2 for further details).

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

In the event of an overdose, the Investigator should:

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

8.5 PHARMACOKINETICS

Serum samples will be collected for *RO7172508* PK analyses for both IV and SC administrations.

Mandatory blood samples to evaluate concentrations of study treatment will be collected from an IV line from the arm opposite to that used for study treatment administration. The date and time of each sample collection will be recorded in the eCRF. RO7172508 concentrations will be analyzed by using a validated assay. The PK samples will be taken as outlined in the SoA (see Section 1.3). During the course of the study, PK sampling time-points may be modified on the basis of emerging data to ensure the PK of RO7172508 can be adequately characterized (but without increasing overall blood collection volume for PK). Additional PK samples will be taken at the time of treatment discontinuation, if the participant experiences an infusion-related AE (such as an IRR, CRS), or if the participant experiences an AE leading to dose-reduction or delay of RO7172508 administration (see Section 6.6 Dosage Modifications).

Remaining volumes of PK samples may also be used for assay development or validation, for RO7172508-related exploratory analyses, or to help develop further blood tests, after they are used for the mentioned intended uses.

Serum samples will be collected for obinutuzumab PK analyses in those participants who receive obinutuzumab as pre-treatment.

sCEA will be measured as outlined in the SoA tables to investigate the impact on quantification of RO7172508 levels by the PK assay.

The PK samples will be destroyed within 2 years after the date of final Clinical Study Report (CSR), unless the participant agrees to participate in the RBR. Details on sampling procedures, sample storage, and shipment are given in the Study Flow Chart and Laboratory Manual.

8.5.1 Immunogenicity Assessments

As RO7172508 is a human antibody, there is a risk that ADAs against RO7172508 could develop, potentially reducing its efficacy and/or potentially resulting in symptomatic hypersensitivity reaction, in particular immune-complex reactions.

Antibodies to RO7172508 will be evaluated in blood samples collected from all participants according to the SoA (Section 1.3). Additional ADA samples should also be collected at the time of treatment discontinuation or at the safety follow-up visit. In each case, for each collected ADA sample, a corresponding PK sample will be collected at the same time-point for the determination of the RO7172508 concentration. *Participants experiencing a Grade ≥3 toxicity potentially related to ADAs will not be further treated with RO7172508 (see Section 7.1).*

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against RO7172508. The date and time of each sample will be recorded in the eCRF.

Remaining volumes of ADA samples may also be used for assay development or validation, for compound-related exploratory analyses, or to help develop further blood tests, after they are used for the mentioned intended uses.

Antibodies to obinutuzumab will be evaluated in all participants who receive obinutuzumab as pre-treatment according to the SoA.

The PK/ADA samples will be destroyed within 2 years after the date of final CSR, unless the participant agrees to participate in the RBR.

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

8.6 PHARMACODYNAMICS

The PD outcome measures for this study are:

- **Whole blood samples:** Peripheral blood immune cells will be assessed with respect to the changes in the characteristics of lineage (CD4+ T-cells, CD8+ T-cells, NK cells, monocytes, T-regulatory cells, and B-cells), activation (including but not limited to HLA-DR, etc.), differentiation (including but not limited to Ki67, etc.) and TCR Vβ repertoire changes.
- **Serum and/or plasma samples:** PD biomarkers such as cytokines and inflammation markers (including but not limited to TNFα, IFNγ, IL-6, *Macrophage Inflammatory Protein [*MIP*]*, etc.) will be analyzed. Because these measurements are also safety measure assessments during any IRRs, they will be examined in participants enrolled in both Part I and Part II of the study. Disease-monitoring markers that include but are not limited to sCEA will also be assessed.
- **Archival tissue and fresh tumor biopsy:** Study enrollment will be based on CEA status assessed on archival tissue (*with the exception of participants with CRC). I*f archival is not available, fresh biopsy collected at baseline will be used. Mandatory tumor biopsy samples obtained in Part II *for all participants (including participants with CRC)* at baseline and on-treatment (Cycle 2 Day 8; see SoA, Section 1.3) will be assessed for changes in immune cell numbers and activation characteristics as well as changes in tumor markers such as PD-L1. These analyses will be performed by flow cytometry, molecular and/or immunohistochemistry methods with respect to changes in the characteristics of lineage (CD4+ T-cells, CD8+ T-cells, NK cells, monocytes, T-regulatory cells, and B-cells), activation (including but not limited to CD25, CD69, etc.), differentiation (including but not limited to Ki67, PD1, TIM3, ICOS, etc.), and TCR Vβ repertoire.

Whole blood, serum/plasma, and tissue samples will be collected at time-points specified in the SoA (Section 1.3) *and may be modified or reduced based on emerging data. The number of samples will not exceed what is described in the SoA.*

Residual blood, serum/plasma and tissue samples may also be used for additional (assay) validation experiments after the specified analyses were performed.

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

These samples will be destroyed within 2 years after the date of final CSR unless the participant gives specific consent for the remainder of the sample(s) to be stored for optional exploratory research within the RBR (see Section 8.8.1).

8.7 GENETICS

Whole blood samples for genetics will be taken at the time-points mentioned in SoA (Section 1.3). These samples will be destroyed no later than 2 years after the date of final CSR, unless the participant gives specific consent for the remainder of the residual material to be stored for optional potential exploratory research within the RBR (see Section 8.8.1).

The results of such specimen analysis will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future. The specimens will also be made available for future biomarker research towards further understanding RO7172508, treatment of related diseases and AEs.

See RBR (Section 8.8.1) for related pharmacogenomics or genetic analysis.

8.7.1 Clinical Genotyping

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

The DNA may be used to identify biomarkers that are predictive of response to treatment with RO7172508, and will help to better understand the pathogenesis, course, and outcome of the studied cancer types. Genes associated with immunity, including but not limited to KIR, HLA, etc. and how these impact on the PK, PD, efficacy, or safety of the study treatment will be explored. This may include genome sequencing, to investigate biomarkers that might predispose the participant for drug-associated autoimmunity or to a positive tumor response following study treatment. These assessments will be performed if safety or efficacy rationales develop.

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

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

8.7.2 Whole Genome/Exome/Targeted DNA Analysis

Archival tumor tissue, fresh tumor tissue sample and blood will be collected at the visits specified in the SoA and may be used for DNA and/or ribonucleic acid (RNA) extraction for exploratory research on genomic biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways, or immune-related markers [e.g., T-cell receptor sequence/TCR Vβ], microsatellite instability [MSI] and tumor mutation burden), and for DNA and/or RNA extraction to enable genomic analysis for exploratory research on genetic biomarkers.

8.7.2.1 Transcriptome Analysis

Blood and tissue samples may be used for potential RNA extraction and subsequent gene expression profiling to enable:

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

8.8 BIOMARKERS

The specimens will be used for research purposes to identify biomarkers useful to predict and monitor response to RO7172508 treatment, identify biomarkers useful to predict and monitor RO7172508 safety, assess PD effects of RO7172508 treatment, and investigate potential mechanism of therapy resistance. Additional markers may be measured in case a strong scientific rationale for these analyses develops.

Whole blood, serum/plasma, and tissue samples will be collected at time-points specified in the SoA (Section 1.3). See Section 8.6 for additional details.

Tumor

Mandatory tumor biopsy samples (each time-point consisting of at least two tissue specimens [preferably three]) will be collected from all participants who participate in Part II of the study on two occasions (once at baseline and once during the study treatment period [C2D8]). Collection of tumor biopsies will be guided by ultrasound or CT scan using a 16-gauge needle to provide cores of at least 20 mm in length. Three core biopsies will be obtained from all participants.

Cytological, fine needle aspiration or biopsy of bone lesions is not acceptable.

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

Archival tumor tissue is to be obtained from all participants, if available, in order to perform CEA assessment for participant eligibility *except for participants with CRC* (refer to the Laboratory Manual). Both archival and fresh tumor biopsy specimens will be analyzed with respect to changes as described (Section 8.6) including but not limited to immune and tumor cell characteristics, TCR Vβ repertoire etc.

Whole Blood

In Part II of the study during dose-escalation, whole blood samples will be collected for flow cytometry for determination of immune cell markers (including but not limited to immune cell subsets, activation and proliferation markers). A whole blood sample will be taken for TCR Vβ sequencing (the CDR3-TCR beta chain repertoire). The DNA will be used to determine in peripheral T-cells the repertoires of TCR Vβ CDR3 and analyze TCR diversity.

Serum and/or plasma

Blood for serum/plasma isolation will be collected in Part I and Part II for investigation of markers and cytokines including but not limited to sCD25, IL-6, IFNγ, TNFα and others, and soluble tumor markers including but not limited to sCEA, etc. In the event of an IRR, an additional sample will be collected.

Clinical Genotyping Samples

From every participant in Part II, a baseline mandatory whole blood sample will be taken for DNA/RNA extraction. The DNA will be used to determine if alleles at genes associated with immune responses such as chemotaxis, HLA, immunosuppression, etc, affect the PK/PD/efficacy/safety of RO7172508. Data arising from this study will be subject to the same confidentiality as the rest of the study.

Other Safety Biomarkers

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

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

8.8.1 Samples for Research Biosample Repository

8.8.1.1 Overview of the Research Biosample Repository

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

8.8.1.2 Sample Collection

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

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

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

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

Leftover of sample derivatives such as DNA and RNA

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

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

Samples may be sent to one or more laboratories for analysis for WGS/WES and other genomic analyses 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. The participant will not be identified by name or any other personally identifying information. WGS/WES data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies to increase researcher's understanding of disease pathobiology and guide the development of new therapeutic approaches. Given the complexity and exploratory nature of these analyses, WGS/WES data and analyses will not be shared with Investigators or study participants unless required by law.

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate Laboratory Manual.

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

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

8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

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

8.10 TIMING OF STUDY ASSESSMENTS

8.10.1 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 participants and for participants who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments 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 (ESF) 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 Cycle1 Day 1 unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle1 Day 1 may be used (and do not need to be repeated for screening).

8.10.2 Assessments during Treatment

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

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

8.10.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the study or discontinue from the study early (e.g., due to progressive disease) will be asked to return to the clinic 28 days after the last dose of study treatment for a follow-up visit. The visit at which a response assessment shows progressive disease may be used as the study completion/early termination visit. Refer to Section 1.3 for the schedule of activities.

8.10.4 Follow-Up Assessments

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

8.10.5 Assessments at Unscheduled Visits

Please see the SoA (Section 1.3) for activities that are required to be performed in case of an unscheduled visit.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Not applicable

9.2 SAMPLE SIZE DETERMINATION

Part I will enroll up to approximately 5 participants. The sample size is determined by the dose-increment steps implemented in this part.

In Part II, it is anticipated that a maximum of approximately 60 participants will be enrolled in each dose-escalation phase (IV and SC) (up to approximately 75 participants if one or several cohorts are expanded). *In case the OBD dose cohort is expanded both with and without obinutuzumab, an additional 15 participants may be enrolled.*

The probability of observing at least one event out of 15 participants for a true underline rate of 10% is 79% while out of 5 patients is 41%. Probabilities of the occurrence of 1 or more events for different ranges of true underline rates and different participant numbers are summarized in Table 20.

The exact sample size for the dose-escalation part cannot be pre-determined and depends on the number of cohorts needed to reach the MTD (or highest safe dose if MTD is not reached).

Table 20 Probabilities for Observing Adverse Events

Total N of Participants	*True AE Probability*	*Probability that AE ≥ 1*	*Probability that AE ≥ 2*	*Probability that AE ≥ 3*
15	*0.1*	*0.79*	*0.45*	*0.18*
	0.2	*0.96*	*0.83*	*0.60*
	0.3	*1.00*	*0.96*	*0.87*
	0.4	*1.00*	*0.99*	*0.97*
	0.5	*1.00*	*1.00*	*1.00*
10	*0.1*	*0.65*	*0.26*	*0.07*
	0.2	*0.89*	*0.62*	*0.32*
	0.3	*0.97*	*0.85*	*0.62*
	0.4	*0.99*	*0.95*	*0.83*
	0.5	*1.00*	*0.99*	*0.95*
5	*0.1*	*0.41*	*0.08*	*0.01*
	0.2	*0.67*	*0.26*	*0.06*
	0.3	*0.83*	*0.47*	*0.16*
	0.4	*0.92*	*0.66*	*0.32*
	0.5	*0.97*	*0.81*	*0.50*

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 21.

Table 21 Analysis Populations

Population	Description
Efficacy	All participants who received at least one dose of RO7172508.
Safety	All participants enrolled in the study who received at least one dose of study treatment *(RO7172508 and/or obinutuzumab if applicable)* will be included in the safety population. Unless otherwise specified, the safety population will be the default analysis set used for all analyses.
DLT evaluable	DLT–evaluable participants are those who have completed the DLT window without a DLT, or participants who reported with a DLT. This population will be used in the determination of the MTD.
Pharmacokinetic	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
Immunogenicity	Participants who had at least one pre-dose and one post-dose ADA assessment will be included and analyzed according to the treatment they actually received. The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

9.4 STATISTICAL ANALYSES

The data will be analyzed by the Sponsor and/or designated Contract Research Organization (CRO). Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and biomarker measurements. Data will be summarized by cohort and regimen within each part and CEA level where applicable*, including the additional participants that may be enrolled in expanded cohorts (see Section 4.1.2.2). Participants who receive only obinutuzumab but no dose of RO7172508 will be summarized separately.*

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment *(RO7172508 or obinutuzumab (if applicable) as appropriate)*.

The following endpoints may be used to select a route of administration for further development: PD parameters including T-cell activation in blood and in the tumor; pharmacokinetic parameters such as AUC, C_{max} and half-life; tolerability and safety; as well as incidence of ADAs and their effect on exposure. Clinical efficacy will be considered, but is not expected to be a key criterion, as efficacy will likely be affected by parameters which cannot be controlled for in such small cohorts. Data will be listed and summarized by dose group as described in this analysis section. Analyses are exploratory in nature and no formal hypothesis testing will be performed.

If one route of administration is not unequivocally superior, and a decision cannot be taken during or at the end of dose escalation, both routes of administration will be compared in disease specific expansion. Criteria for selection of a route of administration will then be added via the amendment preceding the expansions, including endpoints.

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 will include all participants in the efficacy population with participants grouped according to cohort (and schedule if applicable) within each study part. Primary, secondary, and exploratory endpoints are described in Section 3.

The efficacy endpoints of ORR, DCR and PFS according to RECIST v1.1 will be evaluated using the methods described in Table 22:

- Objective response is defined as a CR or PR, as determined by the Investigator's assessment using RECIST v1.1 and confirmed by repeat assessments ≥ 4 weeks after initial documentation. To classify a response as SD, measurements will have to be classified as stable (according to RECIST v1.1) at least once after study entry at a minimum of 6 weeks after study entry.
- ORR and DCR are both determined as the rate of participants with an observed tumor response of CR or PR (ORR) or CR, PR or SD (DCR). ORR and DCR will be derived for RECIST v1.1.
- Among participants with an objective response (responders), DOR will be defined as the time from first occurrence of a documented objective response until the time of documented disease progression or death within 30 days from last study treatment from any cause during treatment, whichever occurs first. Censoring methods will be

the same as the one applied for PFS (on-study drug treatment). This will be calculated for participants who have a best overall response of CR or PR as defined per RECIST v1.1 and per iRECIST.

- PFS (on-treatment) will be defined as the time from study treatment initiation (Cycle 1 Day 1) to the first occurrence of documented disease progression or death from any cause during treatment (death within 30 days from last study treatment), whichever occurs first. For participants who do not have documented progressive disease or death during the study, PFS will be censored at the day of the last tumor assessment. If no post study drug treatment tumor assessment is available, PFS will be censored at the day of the first study drug administration + 1 day.
- OS is defined as the time from the first dose of study treatment to the time of death from any cause on study. 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).

Table 22 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
• ORR • DCR • DOR • PFS (on-treatment) • According to RECIST v1.1 criteria and iRECIST	No formal statistical model and no formal hypothesis testing are planned in this study. Tumor response data will be reported using descriptive statistics. Response data will be listed. Participants with missing or no response assessments will be classified as not evaluable unless there is documented clinical deterioration, in which case participants will be classified as non-responders. Reasons for non-evaluability will be summarized (e.g., withdrawal of consent, study discontinuation because of AE or physician decision). ORR and DCR will be summarized by using relative frequencies and 90% confidence interval (CI). Duration of response and PFS (on-treatment) will be summarized by using time-to-event analyses and Kaplan-Meier curves.
• OS	OS data may be tabulated and summarized using time-to-event analyses and Kaplan-Meier curves if data are collected and mature. Summaries will be carried out by cohort (and schedule if applicable) separately for each part. Response data will be listed. This will be carried out for RECIST v1.1 (secondary efficacy endpoints) and iRECIST (exploratory efficacy endpoints).

An exploratory assessment of tumor kinetic modelling may be performed by comparing on-treatment and post-treatment scans with at least two pre-treatment scans not older than 12 weeks prior to Cycle 1 Day 1, if available. For this exploratory assessment, all measurable lesions should be reported. The two pre-treatment scans consist of a pre-study scan and the study baseline scan and will allow estimation of depth and duration of response on target lesion size due to RO7172508 and the effect of

RO7172508 on the risk of the appearance of new lesions during the treatment period. Data will be explored by using linear and/or exponential models, as appropriate, in non-linear mixed effect modeling software, and this exploratory assessment of tumor kinetic modelling will be performed if the data collected allow it.

This will be presented separately from the main clinical study report (CSR).

9.4.3 Safety Analyses

Unless otherwise specified, the safety population will be the default analysis set used for all analyses. *Those participants who receive only obinutuzumab, but withdraw from the study before receiving RO7172508, will be summarized separately.*

DLT evaluable participants will be used in the determination of the MTD.

The safety endpoints and appropriate analyses are summarized in Table 23.

Table 23 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. 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 Section 3.1 of Appendix 2. AEs will be summarized by mapped term and appropriate thesaurus level. Toxicity grade, seriousness and relationship to study treatment will be presented, as well as *listings* of deaths, AEs leading to death and premature withdrawal from study treatment. Glossary of AEs, medication and procedures will be provided. *AE occurring between obinutuzumab pre-treatment (if applicable) and the first administration of RO7172508 will be summarized separately.*
Nature and frequency of DLTs	DLT events will be presented by individual listings. The MTD will be estimated by the mCRM-EWOC using DLT evaluable participants. The MTD estimate will be presented along with 90% Credible Intervals.
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; Système International d'Unités) by individual listings with flagging of abnormal results. Shifts in NCI CTCAE v5.0 grades from baseline to the worst grade observed during treatment and summary tables of change from baseline over time based on SI units will be presented for selected laboratory parameters. Individual participant listings (abnormal values or out of range) will be produced. See Appendix 4 for details on standard reference ranges and data transformation and the definition of laboratory abnormalities. Additional figures/tables/listings will be produced as deemed appropriate.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	Abnormal 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 participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms. Concomitant medications will be presented in summary tables and listings.
Exposure to study medication	Exposure to study medication will be summarized by total duration of study medication, number of cycles started and cumulative dose using descriptive statistics. Dose interruptions and their reasons will be presented by schedule and dose level.

9.4.4 Pharmacokinetic Analyses

PK parameters will be read directly from the serum concentration-time profiles or calculated by using standard non-compartmental methods. Estimates for PK parameters,

including C_{max}, AUC, $t_{1/2}$, minimum drug concentration (C_{min}), *clearance (*CL*)* and volume of distribution at steady state (V_{ss}) will be tabulated and summarized.

Analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) separately by group or cohorts.

Individual and mean serum RO7172508 concentration versus time data will be tabulated and plotted by dose-level. Graphical displays of PK data may also be provided.

Monitoring and characterization of ADA responses and their potential impact on PK will also be investigated.

In addition, data may be analyzed using population PK modeling; results will be reported separately.

Individual and mean serum obinutuzumab concentration versus time data will be tabulated.

9.4.5 Immunogenicity Analyses

Antibodies to RO7172508 will be evaluated in blood samples collected from all participants using appropriate assays.

Listings and/or summaries will be prepared for results from screening, confirmatory, and/or titer assays employed to detect ADAs against to RO7172508.

Monitoring and characterization of ADA responses and their potential impact on PK, PD, safety, and efficacy of RO7172508 will also be investigated.

Antibodies to obinutuzumab will be evaluated in blood samples using appropriate assays from all participants who receive obinutuzumab as pre-treatment.

Additional analyses may be conducted as appropriate.

9.4.6 Pharmacodynamic Analyses

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

The PD analysis will be based on the availability of evaluable blood or tumor samples.

All PD parameters will be listed by participant and tabulated by dose-level/regimen and time-point. Descriptive statistics will be used in summarizing peripheral blood and tumor PD markers.

Absolute and percentage change from baseline will be calculated for the PD markers. Graphical techniques will be employed to better understand the relationship of the PD markers with dose and time. Correlations between PD markers, PK of RO7172508, and clinical response will be assessed through data tabulations and graphical techniques. The potential prognostic value of the PD markers may also be investigated.

Correlations between the CEA expression level and pharmacodynamics and efficacy outcomes will be explored using graphical and modelling techniques.

9.5 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed.

10. REFERENCES

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as Appendix 1 (for regulatory, ethical and study oversight considerations), Appendix 2 (for AE definitions, reporting) and Appendix 3 (procedures for recording AEs), Appendix 5 (contraceptive guidance and collection of pregnancy information). Additional study-related appendices are in order of appearance in the protocol.

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/IEC by the Principal Investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/IEC.

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

The Investigator should follow the requirements for reporting all adverse events 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/IEC, 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/IEC submission. The final IRB/IEC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant’s legally authorized representative.

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

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

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

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

A participant who is re-screened is not required to sign another ICF unless a newer version is available or if the re-screening occurs beyond 60 days from the previous ICF signature date.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their specimens 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 specimens. Participants who decline to participate will not provide a separate signature.

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

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

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

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/IEC) 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 specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from Study BP40092 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study BP40092. 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.

Confidentiality for Research Biosample Repository

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

Data derived from RBR specimen 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 specimen data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Monitoring and Oversight Research Biosample Repository

Specimens 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 specimens as specified in this protocol and in the Informed Consent Form. Roche Monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/IEC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5. FINANCIAL DISCLOSURE

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

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

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

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

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

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

Study Monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.2. 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, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

2.1.3. Use of Computerized Systems

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

2.2. RETENTION OF RECORDS

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

2.3. STUDY RECORDS

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

Roche shall also submit an Annual Safety Report once a year to the IEC and competent authorities 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/IEC and to regulatory authorities in accordance with local regulatory requirements.

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

2.3.2. Publication Policy

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

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

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

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

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

2.3.3. 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/IECs to inspect facilities and records relevant to this study.

3. STUDY AND SITE CLOSURE

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

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

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

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

1. DEFINITION OF ADVERSE EVENTS

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

An adverse event can therefore be:

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

Events Meeting the AE Definition:

- Any deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

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

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

- **Results in death.**
- **Is life-threatening.**
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

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

  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - Disability means substantial disruption of the participant's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.
- **Other significant events**:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may

jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

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

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

There may be instances when copies of medical records for certain cases are requested by 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 and/or Medical Monitor.

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

3.1. ASSESSMENT OF SEVERITY

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

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

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

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 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).

[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 participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 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.

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 (where applicable).
- 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 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

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

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5)
- Accidental overdoses or medication errors (see Appendix 2, Section 5.2 for details on reporting requirements)

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

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

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

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

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

If the Investigator becomes aware of any other serious adverse event occurring after the end of the AE reporting period, if the event 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. All special situations associated with RO7172508, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations 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.

For RO7172508 and tocilizumab each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5.1). For RO7172508, adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

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

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

- *RO7172508 Investigator's Brochure*
- *Obinutuzumab/RO7172508 combination - RO7172508 Investigator's Brochure*
- *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 adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION/INJECTION-RELATED REACTIONS/CYTOKINE RELEASE SYNDROME

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study treatment infusion should be captured as a diagnosis (as per CTCAE v.5.0) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction”. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction/Cytokine Release Syndrome eCRF. If a participant experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction/Cytokine Release Syndrome eCRF.

1.2. OTHER ADVERSE EVENTS

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

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

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

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

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

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

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the 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 adverse event is one that resolves between participant evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

4. ABNORMAL LABORATORY VALUES

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

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

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

5. ABNORMAL VITAL SIGN VALUES

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

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

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

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

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

6. ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, Investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN or $>3\times$ baseline value in combination with total bilirubin $>2\times$ULN or $>2\times$ baseline value.
- Treatment-emergent ALT or AST $>3\times$ULN or $>3\times$ baseline value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 8.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 8.3.6).

7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor. This includes death attributed to progression of disease.

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 DISEASE

Medical occurrences or symptoms of deterioration that are anticipated as part of disease progression should be recorded as an adverse event if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of disease on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated tumor growth/development”).

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 criteria (e.g., RECIST v1.1). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to progressive disease, it should be reported as an adverse event.

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 2), except as outlined below.

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

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

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

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

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

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

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory unless otherwise specified.

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

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

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
Clinical Chemistry	• Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH, C-reactive protein, amylase, lipase. (Tryptase: safety only)
Coagulation	• INR, aPTT, PT, Fibrinogen, D-Dimer.
Viral Serology (screening only)	• 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.
Quantitative Immunoglobulins	• IgE (safety only)
Pregnancy Test	• All women of childbearing potential (including those who have had a tubal occlusion) will have a blood pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.
Urinalysis	• Specific gravity • Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. • 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), if blood or protein is abnormal.
Other Tests	• sCEA*

*will be performed centrally *and locally*

The results of each test must be entered into the CRF.

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most 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, 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 each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

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

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

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

i) Pre-menarchal

j) 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.

k) Post-menopausal female

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

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

2. CONTRACEPTION GUIDANCE

- **Female Participants**

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

Table 1 Highly Effective Contraceptive Methods

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

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

3. PREGNANCY TESTING

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

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

4. COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

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

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- **Female participants who become pregnant**

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

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2.

While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment and be withdrawn from the study.

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 a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

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

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant or female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 8.3).

Appendix 6
New Response Evaluation Criteria in Solid Tumors [RECIST] – Version 1.1

Modified Excerpt from Original Publication with Addition of Supplementary Explanations [1]

1. MEASURABILITY OF TUMOR AT BASELINE

1.1. DEFINITIONS

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

1.1.1 Measurable Tumor Lesions

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

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

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

1.1.2 Non-measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical exam that 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 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. Study protocols should detail the conditions under which such lesions would be considered measurable.*

1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

1.2.1 Measurement of Lesions

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

1.2.2 Method of Assessment

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (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.

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

2. TUMOR RESPONSE EVALUATION

2.1 ASSESSMENT OF OVERALL tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed in Section 1.1.1).

2.2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where participants have only one or 2 organ sites involved a maximum of 2 (one site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is ≥10 mm by CT scan).

Target lesions should be selected 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 x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (see also Section 2.3.4).

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: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, 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 below. 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 are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of progressive disease.

For example, if a participant had a baseline sum of 50 mm with 3 measured lesions and during study only 2 lesions were assessed, but those gave a sum of 80 mm, the participant will have achieved progressive disease status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" because the participant is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Table 3 Best Overall Response when Confirmation is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.3 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the 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 shown in Table 1 and Table 2 of this Appendix.

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

In studies where participants with advanced disease are eligible (ie, primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

References

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-247.

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 timepoint per iRECIST are also summarized below. Of note, overall response per iRECIST will not be captured in the electronic Case Report Form (eCRF), but will instead be calculated programmatically by the Sponsor 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 timepoints after disease progression per RECIST v1.1, according to RECIST v1.1 conventions.

NON-TARGET LESIONS

Non-target lesions selected at baseline should continue to be followed at all tumor assessment timepoints after disease progression per RECIST v1.1. At each timepoint, non-target lesions should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" (progressive disease [PD]), or "present without unequivocal progression" (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (eg, non–lymph node lesions must be ≥10 mm on the longest diameter; new lymph nodes must be ≥15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint should be measured from that point on, if the maximum number of measurable new lesions has not been reached. However, for calculation of the sum of diameters for new lesions, iRECIST excludes measurements from new lesions that were not measurable at first appearance.

All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

<u>Note regarding new lymph node lesions</u>: If at first appearance the short axis of a lymph node lesion is ≥15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥10 mm and <15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is <10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to <15 mm (or even <10 mm).

Table 1 Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	*Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1*
Target lesions	*Measurements should be continued according to RECIST v1.1 conventions.*
Non-target lesions	*Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (PD), or present without unequivocal progression (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.*
New lesions	*New lesions should be evaluated for measurability per RECIST v1.1.* *All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.* *Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint.* *All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.*

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*

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

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Appendix 8
Supporting Statistical *Documentation*

1 MONOTHERAPY DOSE-ESCALATION

This appendix provides details of the design that will guide the monotherapy IV dose-escalation stage of this study and of its operating characteristics through simulations.

1.1 RATIONALE FOR MODEL-BASED DESIGN

The modified Continuous Reassessment Method (mCRM) design uses a statistical model that actively seeks a dose-level close to the maximum tolerated dose (MTD) by using toxicity data from all enrolled evaluable participants to compute a precise dose-toxicity curve. It locates the MTD efficiently and minimizes the number of participants treated at possibly pharmacological inactive dose-levels. Such model-based designs have been successfully applied in many Phase 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.

In this design, the MTD is defined as the dose maximizing the posterior probability that the DLT rate, $\pi(MTD)$, belongs to [0.2, 0.35] while keeping the probability of overdose $P\{p(MTD) > 0.35\}$ below 0.25.

1.2 STATISTICAL MODEL

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

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

where

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

and d^* is the reference dose (in this case $d^* = 100$).

The model thus can be rewritten as:

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

where α and $\log(\beta)$ are assumed to follow a bivariate normal distribution, $\alpha 0 = \alpha$ and $\alpha 1 = \log(\beta)$ are the parameters to be estimated.

1.2.1 Model Prior

For the multiple participant cohort dose-escalation, the prior distribution will be a mixture of prior informative and minimally informative components. The informative component will be the posterior distribution of the CEA TCB ($cibisatamab$) monotheraphy toxicity data (without obitunuzumab pre-treatment), as of cutoff date 20 July 2017, approximated with a bivariate normal distribution. A minimally informative prior «neutral» component will be constructed based on the assumed not toxic and toxic doses. The two components will be mixed in a 10/90% ratio ($pi_1 = 0.25$) (informative prior component 10%; minimally informative component 90%).

$$(\alpha, log(\beta))^{\tau} \sim \pi_1 N_1(\mu_1,\sigma_1) + (1-\pi_1) N_2(\mu_2,\sigma_2)$$

1.2.2 Informative Component

The parameters of the informative component are listed below:

$$\mu = (-1.4199504, -0.7110435)$$

$$\Sigma = \begin{pmatrix} 0.173397 & 0.0023933 \\ 0.0023933 & 7.3526064 \times 10^{-4} \end{pmatrix}$$

The minimally informative component makes the design robust against surprising deviations from the informative component.

A minimally informative prior component will be constructed based on the assumed not toxic and toxic doses. It is conservatively assumed that would be very unlikely (with a 60% confidence) that 10% or higher DLT rates are associated with the first dose of monotheraphy dose-escalation and that it would be very unlikely (with 90% confidence) that a 25% or lower DLT rates are associated with the dose of 400 mg.

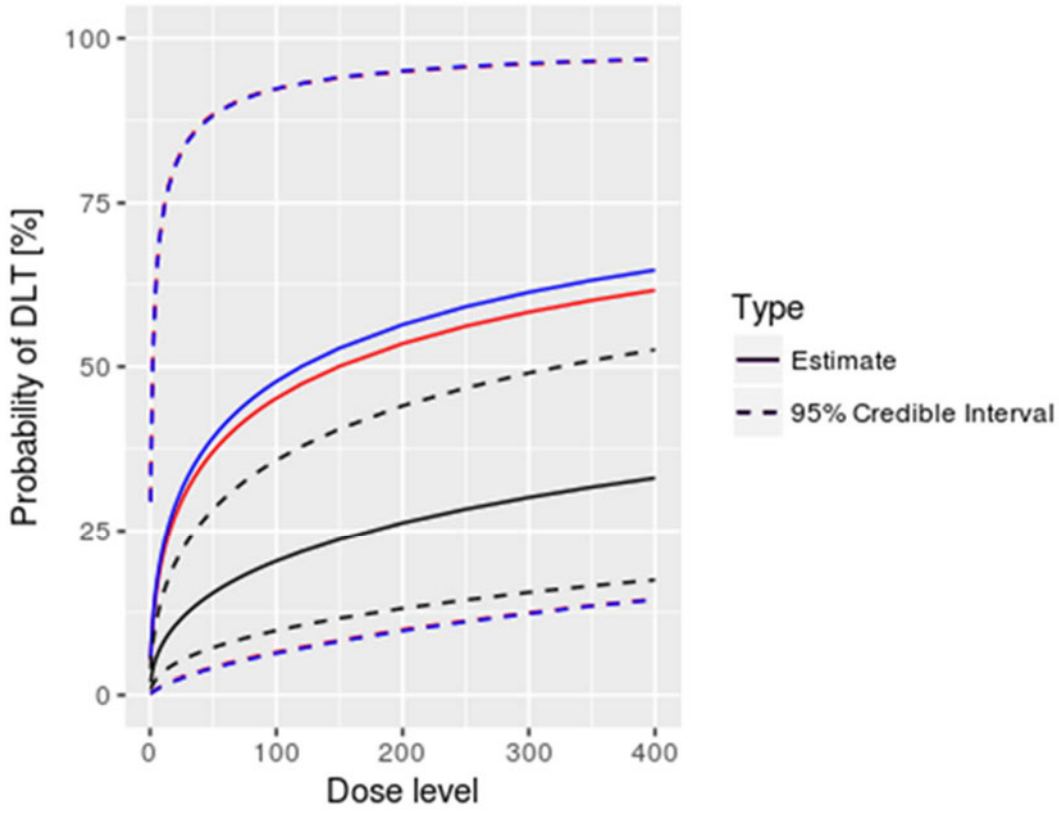
The parameters of the minimal informative prior are listed below:

$$\mu = (-0.0983878, -0.4150429)$$

$$\Sigma = \begin{pmatrix} 1.7525039 & -0.0052047 \\ -0.0052047 & 0.0185343 \end{pmatrix}$$

The plot of the prior distribution used for the study can be seen in Figure 1 and it will be the primary prior distribution used to determine the dose-escalation decisions.

Figure 1: Prior Plot



In black the informative, in blue the minimal informative and in red the mixture prior dose-toxicity relationship.

1.2.3 Dose Grid

The following dose grid has been used: from 0.5, to 10 by 0.1, from 11 to 20 by 1, 25, 27, from 30 to 100 by 5, 120, 150 to 400 by 50.

1.2.4 Maximum Dose-Increments

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

Relative to DLT:

Until 1 DLT an increment of 100%, from 1 DLT an increment of 50% maximum are allowed.

The lower increment between the ones described above will then be chosen as maximum allowed dose-increment.

1.2.5 Stopping Rules

The trial will be halted if either at least 6 participants have been observed at a dose close to MTD (i.e., a dose differs by 20%) and the posterior probability that

[0.2 ≤ Prob(DLT | dose) ≤ 0.35] for the next best dose is above 40% or the maximum of 60 DLT-evaluable participants is reached.

1.3 MODEL PERFORMANCE EVALUATION

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

Table 1: Dose-Escalation Mock Runs

Dose, mg	DLTs	Next Dose, mg	Stop	Increment
1.6	0	3.2	FALSE	100
1.6	1	2.4	FALSE	50
1.6	2	0.8	FALSE	-50
1.6	3	NA	TRUE	NA
3.2	0	6.4	FALSE	100
3.2	1	4.8	FALSE	50
3.2	2	3.1	FALSE	-3
3.2	3	1.3	FALSE	-59
6.4	0	12.0	FALSE	87
6.4	1	9.5	FALSE	48
6.4	2	6.4	FALSE	0
6.4	3	3.9	FALSE	-39
12.0	0	20.0	FALSE	67
12.0	1	18.0	FALSE	50
12.0	2	12.0	FALSE	0
12.0	3	8.3	FALSE	-31
20.0	0	40.0	FALSE	100
20.0	1	30.0	FALSE	50
20.0	2	25.0	FALSE	25
20.0	3	14.0	FALSE	-30
40.0	0	80.0	FALSE	100
40.0	1	60.0	FALSE	50
40.0	2	50.0	FALSE	25
40.0	3	27.0	FALSE	-32
80.0	0	150.0	FALSE	88
80.0	1	120.0	FALSE	50
80.0	2	90.0	FALSE	12
80.0	3	50.0	FALSE	-38
150.0	0	300.0	FALSE	100
150.0	1	200.0	FALSE	33
150.0	2	150.0	FALSE	0

Dose, mg	DLTs	Next Dose, mg	Stop	Increment
150.0	3	95.0	FALSE	-37
300.0	0	400.0	FALSE	33
300.0	1	400.0	FALSE	33
300.0	2	250.0	FALSE	-17
300.0	3	150.0	FALSE	-50

1.4 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.

1.4.1 Dose-toxicity Scenarios

In these simulations (Figure 2), the starting dose of 0.5 mg is assumed. Scenario 1 reflects the current expected toxicity of this compound. The others are intermediate or extreme scenarios. The MTD (upper 35% DLT toxicity interval) ranges from 69 mg (low MTD) to 438 mg (illustrating a scenario for which toxicities are expected only at the highest dose).

Figure 2 Dose Toxicity Scenarios

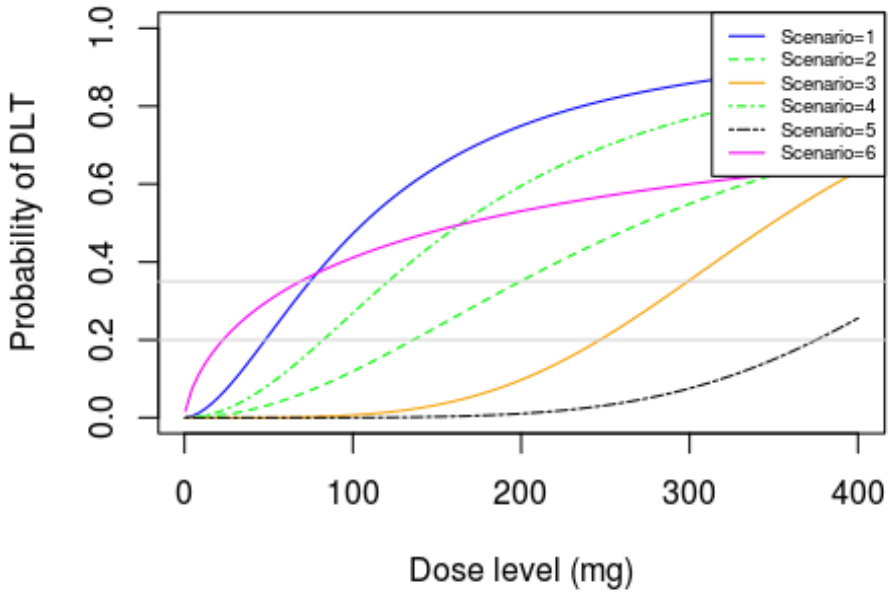


Table 2: Scenarios Parameters

Scenario	Target Dose Interval, mg	Parameters
1	48-75	alpha = -0.11, beta = 1.74
2	136-199	alpha = -2, beta = 2
3	247-299	alpha = -5, beta = 4
4	82-121	alpha = -1, beta = 2
5	375-438	alpha = -8, beta = 5
6	23-69	alpha = -0.36, beta = 0.7

1.4.2 Simulation Results

For each of the scenarios, 500 trials were simulated.

The design is evaluated using the following criteria: the MTD chosen, the number of participants treated at doses higher than the MTD, and the total number of participants treated. The result of the simulations is summarized in Table 3.

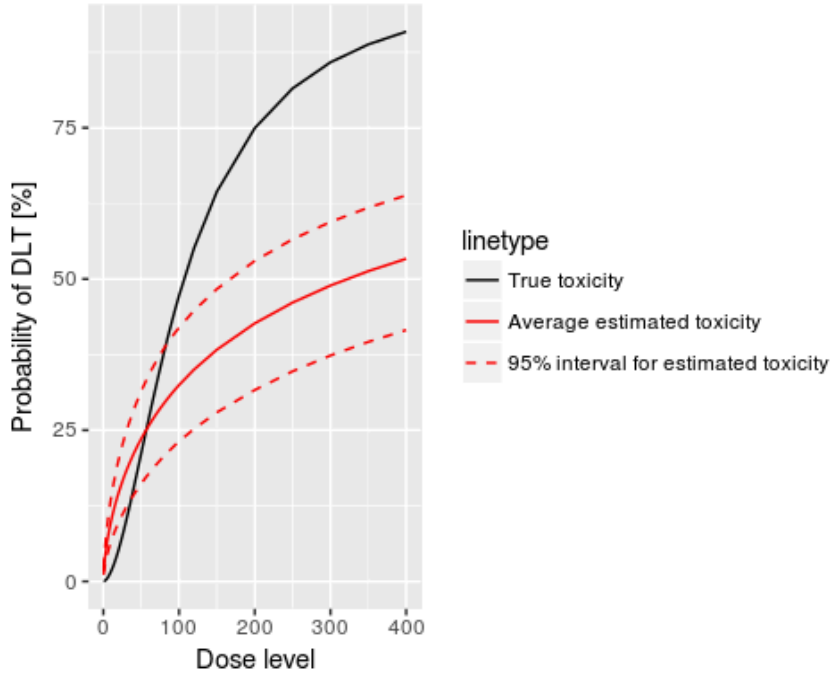
Table 3: Simulation Study Results Summary

Scenario	Target Dose Interval in True Scenario, mg	Overall N of Participants*	N Participants Treated above Target Toxicity Interval*	Proportions of DLTs in the Trials, %*	Doses Selected as MTD, mg*	Dose most often Selected as MTD, mg
1	48-75	29 (24, 36)	7 (0, 12)	16.4 (12.5, 21.2)	72.3 (44.5, 100)	50
2	136-199	34 (30, 39)	6 (0, 12)	13 (10, 16.7)	186.7 (120, 250)	150
3	247-299	34 (30, 39)	6 (3, 9)	10.5 (6.7, 13.9)	290.3 (250, 350)	250
4	82-121	31 (27, 36)	4 (0, 9)	14.8 (11.1, 18.2)	111.7 (75, 150)	150
5	375-NA	37 (33, 45)	0 (0, 0)	7.3 (5.6, 9.5)	384 (350, 400)	400
6	23-69	28 (21, 36)	2 (0, 9)	18.1 (14.3, 22.2)	45.1 (14, 85)	25

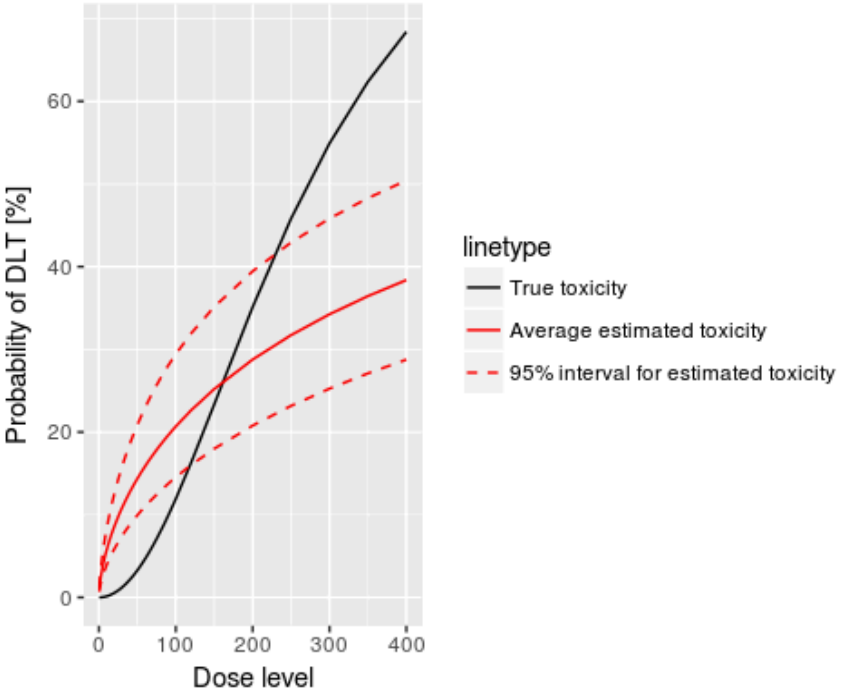
* mean and 10 and 90 % quantiles.

In addition, illustrated here separately for each true dose toxicity scenarios the true toxicity curve from the scenario with the average model fit from the 500 simulation runs.

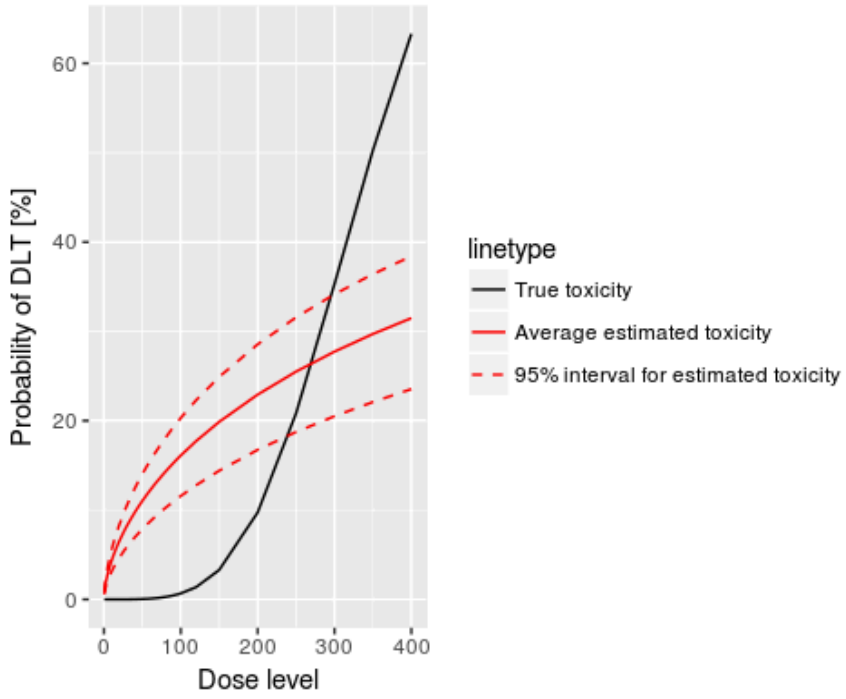
Scenario 1: True MTD 74.64 Parameters alpha=-0.11, beta=1.74



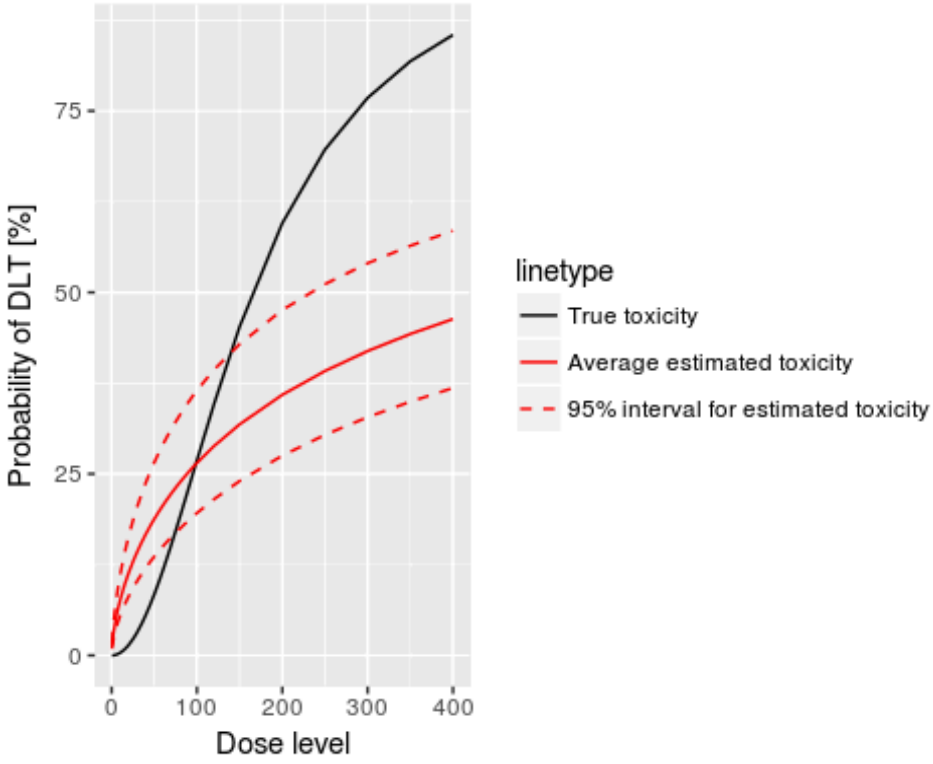
Scenario 2: True MTD 199.47 Parameters alpha=-2, beta=2



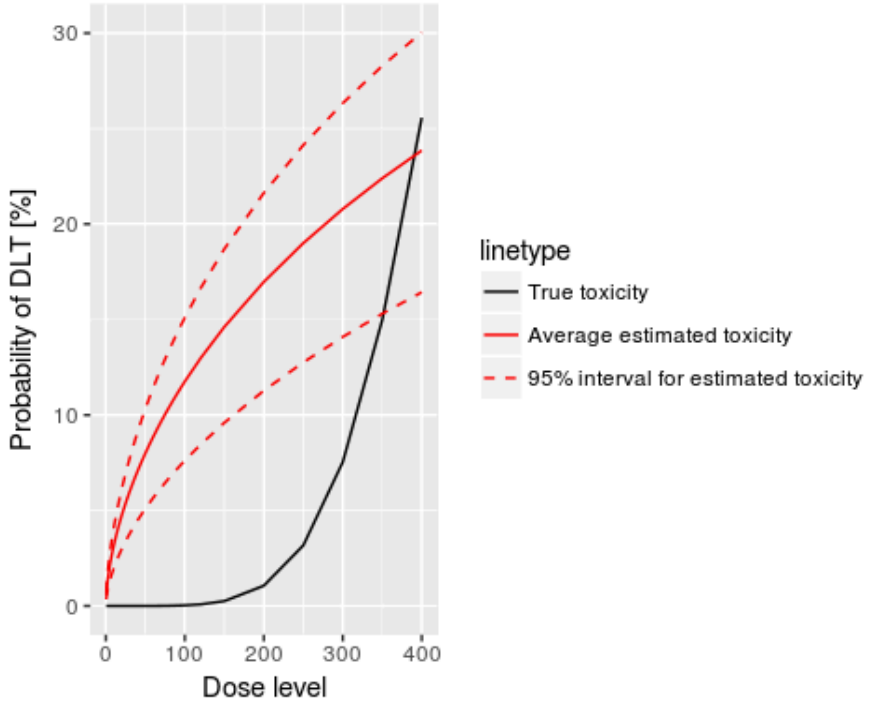
Scenario 3: True MTD 298.99 Parameters alpha=-5, beta=4



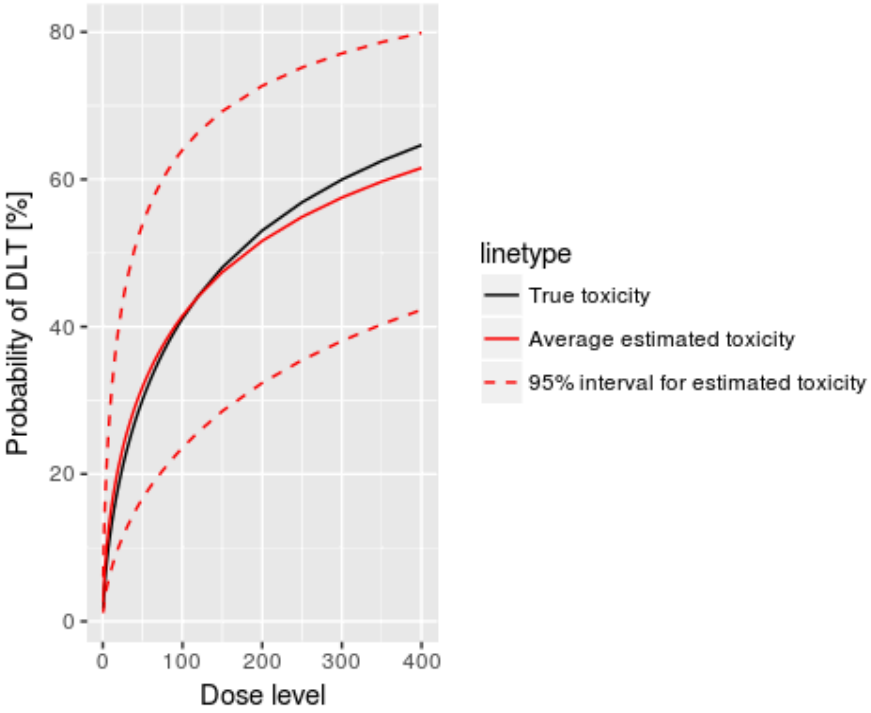
Scenario 4: True MTD 120.98 Parameters alpha=-1, beta=2



Scenario 5: True MTD 437.62 Parameters alpha=-8, beta=5



Scenario 6: True MTD 69.07 Parameters alpha=-0.36, beta=0.7



2 *BAYESIAN POSTERIOR PROBABILITY APPROACH TO THE EVALUATION OF LOSS OF EXPOSURE*

This appendix provides the details of the approach that will be used during the course of the study to evaluate the impact of anti-drug-antibodies (ADAs) on exposure of RO7172508. If a significant number of participants experience a relevant loss of exposure to RO7172508 due to ADAs (LOE+ rate), then obinutuzumab pre-treatment will be implemented. The decision to implement obinutuzumab will be based on a Bayesian posterior probability approach.

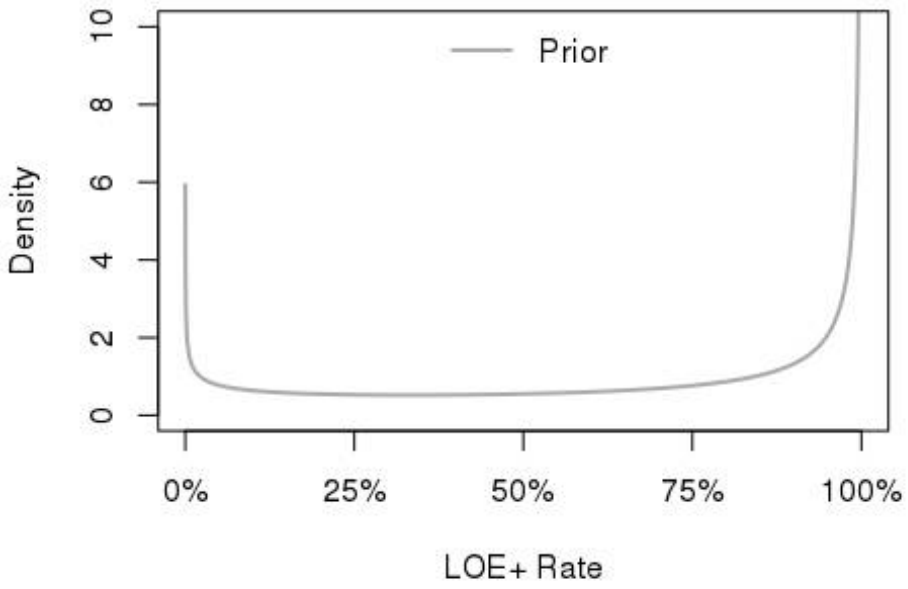
All analyses were performed using the R statistical software R version 3.4.4 (2018-03-15) (@baseR).

2.1 PRIOR DISTRIBUTION

In the Bayesian approach, it is assumed that the prior distribution of the true underling LOE+ rate, $\pi(p)$ (between 0 and 1) , follows a two-parameters beta distribution $\beta(a, b)$ with parameters a and b.

In this case, the parameters are assumed to be a=0.6667 and b=0.3333 and correspond to the prior shown in Figure 1. This prior, representing previous knowledge or belief of the LOE+ rate of the regimen, was based on results observed in participants treated with cibisatamab (CEA-TCB), where 14 out of 21 (67%) in the flat dosing mono-therapy cohorts ≤ 20 mg had experienced loss of exposure due to ADAs (cibisatamab IB v5). This dose range was selected as it is expected to be similar to those administered in the current study. The CEA-TCB data were appropriately down weighted in order to derive the current prior.

Figure 1 *Prior Distribution*



2.2 POSTERIOR DISTRIBUTION AND DECISOPN CRITERIA

As new information from the RO7172508 dose escalation is collected, the prior distribution will be updated to generate the posterior probability distribution of the true LOE+ rate given the data observed. At each assessment, the posterior probability, with n participants who experienced a relevant loss of exposure out of n+m evaluable participants, will therefore follow a two-parameters beta distribution β(a+n, b+m).

At the time of the evaluation, if there is high confidence that the underlying true LOE+ rate is above a pre-defined target, the obinutuzumab pre-treatment will be introduced for all subsequent participants in the study. Otherwise, the dose escalation will proceed without obinutuzumab pre-treatment until the next assessment or the end of the dose escalation (whichever is reached first).

For a given target LOE+ rate, the posterior probability can be computed as:

$$PP = Prob(\text{True LOE + Rate} \geq (\text{Target LOE + Rate/Data, Prior}))$$

Therefore, the decision rule for the implementation of obinutuzumab pretreatment at interim can be constructed as follows:

if $PP > \Theta_H$ *then implement obinutuzumab, otherwise continue.*

The target LOE+ rate has been set to 50%. The posterior probabilities threshold, Θ_H, has been set to 80% based on acceptable probability of implementing obinutuzumab under different assumption for true underling LOE+ rates (see Section 1.3).

The first assessment will be conducted once RO7172508 PK data up to Cycle 3 are available from at least 14 participants across both Part I and II and thereafter after each cohort PK RO7172508 data up to Cycle 3 are available and again at the end of the dose escalation.

At the end of the dose escalation, if the above criteria have not yet been met and, at the same time, there is low confidence (<70% confidence level) that the true underline LOE+ rate is less than 5%, the expansion cohorts at the OBD with and without obinutuzumab will be evaluated. The expansion cohorts will determine if the safety profile and pharmacodynamics effects of the regimens are acceptable with continued RO7172508 exposure.

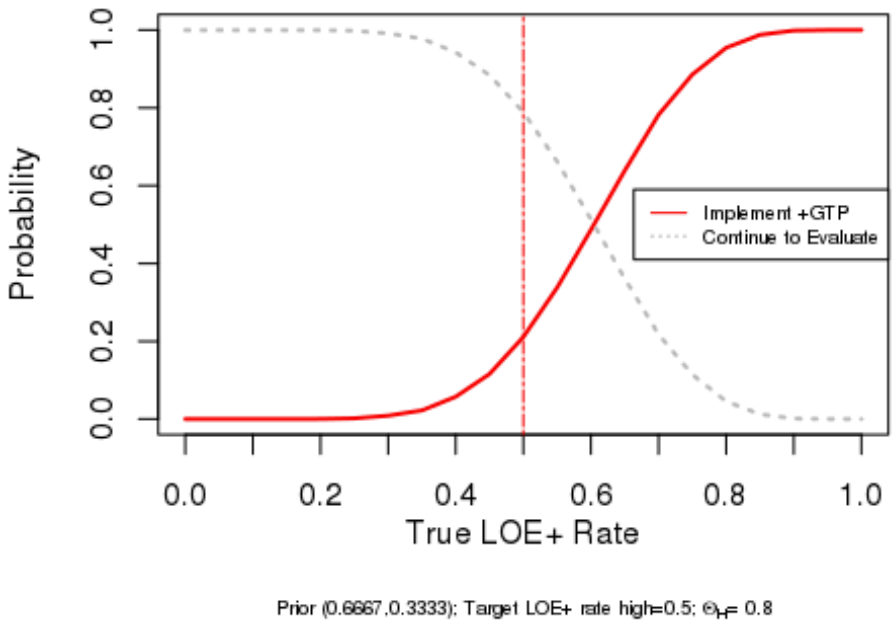
2.3 OPERATING CHARACTERISTICS

The performance characteristics of the study design at the first interim are outlined below.

At the first evaluation, the posterior probability equal or higher than 80% (Θ_H=0.8) that the true LOE+ rate is ≥ 50%, is equivalent to observe 9 or more participants with relevant loss of exposure out of 14 evaluable participants.

The probability of taking the decision to implement obinutuzumab for a given true underline LOE+ rate, based on 10^4 simulations, is illustrated in Figure 2.

Figure 2 *Probability of Implementing Obinutuzumab for Different True Underlining LOE+ rate at N= 14*



If the true underline LOE+ rate is 60% then the decision to proceed exclusively with obinutuzumab pretreatment will be taken in 48.65% of the times. If instead, the true underline LOE+ rate is 40%, then this decision would be taken only in 5.74% of the times.

The exact number of participants, with relevant loss of exposure, required to meet the criteria at subsequent evaluations will depend on the actual number of participants enrolled in each cohort and on the number of cohorts necessary to reach the end of the dose escalation.

For these reasons, an evaluation of the operating characteristics for a meaningful additional number of cohorts (9 cohorts), with constant cohort size (3 participants), is given in Figure 3 based on 10^4 simulations.

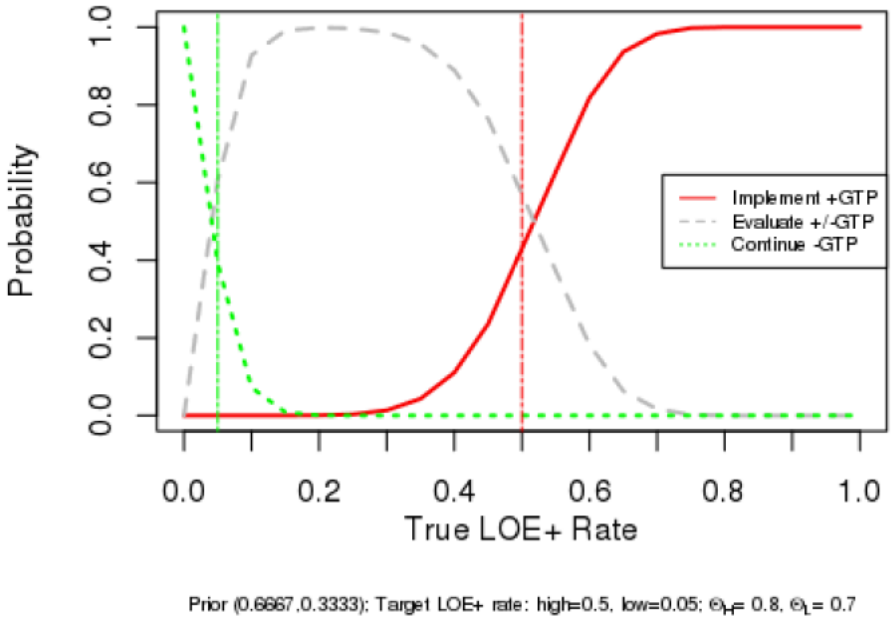
At final analysis with 41 participants the posterior probability equal or higher than 80% (Θ_H= 0.8) that the true LOE+ rate is ≥ 50% is equivalent to observe 24 or more participants with relevant loss of exposure out of 41 evaluable participants.

The posterior probability equal or higher than 70% (Θ_L= 0.7) that the true LOE+ rate is ≤5% is equivalent to observe 1 or less participants with relevant loss of exposure due to ADAs out of 41 evaluable participants

If the true underline LOE+ rate is 60% then the decision to proceed exclusively with obinutuzumab pre-treatment will be taken in 81.81% of the times during the course of the study; if, instead, the true underline LOE+ rate is 40% then this decision would be taken only in 11.06% of the times.

If the true underline LOE+ rate is 5% then the decision to proceed without obinutuzumab pre-treatment at the end of the trial, will be taken in 39.3% of the times.

Figure 3 ***Probability of implementing obinutuzumab for different true underlining LOE+ rate at final analysis N= 41***



Appendix 9 Protocol Amendment History

PROTOCOL AMENDMENT VERSION 3 AND VERSION 4 SUMMARY OF CHANGES

Since the changes made under Protocol BP40092 version 3 and Protocol BP40092 version 4 followed each other in quick succession and Protocol BP40092 version 3 was not submitted to any ethics committees or regulatory authorities, the Summary of Changes provided reflects all changes made under both Protocol BP40092 Version 3 and Version 4.

The protocol synopsis has been updated to reflect the changes of the protocol where applicable.

Section 1.2 Schematic of Study Design

Figure 1 Overview of Study Design has been updated to include obinutuzumab pretreatment for dose escalation.

Section 1.3 Schedule of Activities

Table 1, Table 2, Table 3, Table 4, and Table 5 have been updated, including the footers.

Two new tables (Table 6 and Table 7) Table 6: ***Screening Schedule of Assessments with Obinutuzumab Pretreatment*** and Table 7: ***Schedule of Assessments Part II: Multiple Participant Cohorts SC Q3W*** have been added.

Section 2.1 Study Rationale

[…]

The development of anti-drug antibodies (ADAs) can result in a partial or complete loss of exposure and is thought to be mainly mediated by the stimulation of B-cells, which leads to generation of antibody-producing plasma cells. The use of obinutuzumab as a pre-treatment (if needed) to inhibit or attenuate ADA responses by depletion of B-cells has been implemented in this study and is supported by nonclinical and clinical studies further described in Section 2.2.2. For the benefit/risk assessment of obinutuzumab pre-treatment, please refer to Section 2.3.

Section 2.2.2 *Obinutuzumab*

RO7172508 may induce the production of ADAs that could result in the complete or partial loss of exposure. Obinutuzumab, a humanized and glycoengineered Type II anti-CD20 monoclonal antibody that recognizes the CD20 antigen present on normal and malignant B-cells. Obinutuzumab is approved for the use in untreated and

relapsed/refractory follicular lymphoma as well as untreated chronic lymphocytic leukemia. The use of obinutuzumab has demonstrated effective B-cell depletion following administration in cynomolgus monkeys (Mössner et al 2010) and patients with B-cell malignancies (Salles et al 2012; Cartron et al 2014). The use of obinutuzumab as a pre-treatment to inhibit or attenuate ADA responses in participants with solid tumors is supported by nonclinical and clinical studies. Pre-clinically, obinutuzumab pre-treatment resulted in strong suppression of de novo antibody responses while protective humoral memory responses remained intact both in human CD20 transgenic mice and cynomolgus monkeys. In Studies BP28920 (RO6895882; Phase I), BP29435 (RO6895882 + atezolizumab; Phase Ib) and BP29541 (cibisatamab; Phase I), obinutuzumab pre-treatment effectiveness was confirmed as pre-treated patients did not lose exposure of the investigational compounds. For the benefit/risk assessment of obinutuzumab pre-treatment, please refer to Section 2.3.

For more details on obinutuzumab, please refer to the obinutuzumab IB.

Section 2.3 Benefit/Risk Assessment

[…]

There is a potential risk for RO7172508 to induce the production of ADAs. ADA formation against RO7172508 can potentially reduce its efficacy by blocking CEA or CD3e targeting and/or potentially result in symptomatic hypersensitivity reactions, in particular immune complex reactions. Therefore, Part II of the BP40092 study allows obinutuzumab pretreatment to attenuate the formation of ADAs if a predefined number of patients experience a loss of exposure to RO7172508 (see Section 4.1.3).

If obinutuzumab pretreatment is introduced as a way to mitigate ADA formation and subsequent loss of exposure, the safety profile of RO7172508 given after obinutuzumab will be carefully monitored. Only if the safety profile of RO7172508 after obinutuzumab pretreatment is shown to be acceptable and comparable to RO7172508 alone (i.e., without obinutuzumab pretreatment if applicable) will the Sponsor consider investigating obinutuzumab pretreatment in further development.

Section 3 Objectives and Endpoints

Table 8 Objectives and Endpoints has been updated:

Objectives	Endpoints
Primary	
• To determine the maximum-tolerated dose (MTD) and/or the optimal biological dose (OBD) for intravenous (IV) and subcutaneous (SC) administrations of RO7172508 as monotherapy *and with obinutuzumab pre-treatment (if applicable)*	• Nature and frequency of dose-limiting toxicities (DLTs) and other AEs, PD and PK profile
• To assess the safety and tolerability profile of RO7172508 *and with obinutuzumab pre-treatment (if applicable)*	• Incidence, nature and severity of AEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Secondary	
• To establish the IV and SC pharmacokinetics of RO7172508 given as monotherapy *and with* obinutuzumab *pre-treatment (if applicable)*	The PK profiles and parameters derived for RO7172508 including where appropriate and when data allow, the parameters listed below: • Maximum concentration (C_{max}) • Time of maximum concentration (T_{max}) • Clearance (CL) or apparent clearance (CL/F) (dependent on route of administration) • Volume of distribution *at steady state* (V_{ss}) • Area under the curve (AUC) • Half-life ($t_{1/2}$) • Other PK parameters may be determined, as deemed appropriate.
• To assess the incidence of anti-drug antibodies (ADAs) against RO7172508 *with obinutuzumab pre-treatment (if applicable)*	• Presence or absence and titer of ADAs
• To characterize PD effects and duration of PD response for multiple doses and schedules of RO7172508 administration	• Changes in frequency, activation status and spatial distribution of tumor infiltrating lymphocytes (TILs).

Objectives	Endpoints
• To assess preliminary anti-tumor activity of RO7172508.	• Objective response rate (ORR) • Disease control rate (DCR); defined as rate of response (RR) + stable disease (SD) • Duration of response (DOR) • Progression-free survival (PFS) (on-treatment) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria by Investigator's assessment:

[…]

Tertiary/exploratory	
• To further assess preliminary anti-tumor activity of RO7172508.	• ~~PFS, objective response, DOR, and DCR according to modified RECIST (mRECIST).~~ • PFS, objective response, DOR, and DCR according to immune modified RECIST (iRECIST)Overall survival (OS) • Overall survival (OS).
• To assess ADA specificity	• Development of ADAs directed against either the CEA or CD3 binding moiety.
• To make a preliminary assessment of the efficacy of tocilizumab (Actemra®/RoActemra®) in ameliorating the symptoms of severe CRS following RO7172508 treatment, if data allows.	• Changes in the nature and severity of CRS following administration of tocilizumab for severe CRS.
• *To assess the incidence of anti-drug antibodies (ADAs) against obinutuzumab (if applicable)*	• *Presence or absence and titer of ADAs* • *Serum concentration of obinutuzumab*

Section 4.1 Overall Design

An overview of the study design is provided in Section 1.2.

Study BP40092 is a first-in-human, open-label, multicenter, dose-escalation, Phase I clinical study to determine the maximum-tolerated dose (MTD) and/or the optimal biological dose (OBD) as well as the optimal schedule for intravenous (IV) and subcutaneous (SC) administrations of RO7172508 as monotherapy*, with or without obinutuzumab pre-treatment,* in participants with locally advanced and/or metastatic CEA-positive solid tumors who have progressed on SOC treatment, are intolerant to SOC, and/or are non-amenable to SOC. The study will be conducted in two parts.

[…]

PART II

Part II is a multiple participant cohort/multiple-ascending dose-escalation study to define the MTD and/or OBD of RO7172508 administered as single agent, IV or SC, in participants who have tumors with cytoplasmic and/or membranous CEA expression in ≥ 20% of cells at intensities greater than at least IHC 1+ on archival material (or fresh biopsy when archival is not available). The starting-dose for the initiation of the IV dose-escalation will be determined by Part I and RO7172508 will be initially given Q3W. Dose-escalation will be undertaken based on safety until determination of the MTD or the highest safe dose if MTD is not reached.

~~Once the IV schedule has shown RO7172508 preliminary clinical activity, defined by partial response (PR) or better, according to RECIST (Appendix 6), or the MTD has been established and is greater than 6 mg, the QW SC multiple ascending dose finding cohorts will be initiated. SC dosing will initially be once a week (QW). The starting dose for SC administration will be proposed based on the evaluation of the safety and PK data observed following IV administration; however, due to practical considerations, a minimum dose of 2 mg is defined for a single SC administration. In addition, the QW SC starting dose will not exceed one third of the IV MTD or of the highest safe IV dose tested.~~ *Once the IV schedule has shown RO7172508 preliminary clinical activity, defined by partial response (PR) or better, according to RECIST v. 1.1(Appendix 6), or the MTD has been established and is equal to or above 2 mg, the SC multiple-ascending dose-finding cohorts could be initiated. The starting-dose and regimen (QW or Q3W) for SC administration will be proposed based on the evaluation of the safety and PK data observed following IV administration but will not exceed the highest safe dose tested in the IV Q3W dose escalation; however, due to practical considerations, a minimum dose of 2 mg is defined for a single SC administration. In addition, the QW SC starting-dose will not exceed one third of the IV MTD or of the highest safe IV dose tested.*

Dose escalation in the SC treatment group will proceed until the SC MTD/OBD has been determined (see Section 4.1.2). *If the SC treatment group is started Q3W at a dose <6 mg, the QW schedule can be evaluated once the dose is ≥ 6 mg.* Data from this treatment group will establish if the SC route of administration, which will have a lower C_{max} than IV after first administration, can show comparable efficacy and/or comparable or improved safety profile of a TCB *either QW and/or Q3W.*

During the course of this study, the need for obinutuzumab pretreatment will be assessed based on loss of RO7172508 exposure and/or ADA-related safety events. Details, including decision criteria, are provided in Section 4.1.3 and Appendix ~~7~~8.

[…]

If deemed necessary*, at the end of dose escalation,* to further characterize the safety, preliminary anti-tumor activity, PK, and/or PD profile of RO7172508 (IV and/or SC) *with or without obinutuzumab pre-treatment*, additional participants (up to approximately 15 participants) may be enrolled at the doses already tested*;* or at doses that have not been explored for the determination of the MTD, but not higher than MTD*;* or the highest safe dose tested if MTD has not be determined. *The additional patients could be allocated to one or more doses; however, the total number will not exceed 15 participants across all doses. If new cohorts are opened at a dose equal to or lower than already explored, the cohorts will follow the same recruitment rules and safety windows as per dose escalation rules. Patients enrolled at dose levels that have already been assessed, will also be staggered as per dose escalation rules (i.e. at least one day between consecutive patients). If DLT events are observed, the estimated MTD and the probability of overdosing at the current recruiting cohort, will be re-assessed with all available data. If the updated estimated MTD indicate that the current recruiting cohort is not safe, recruitment will be stopped.*

Section 4.1.2.2 Part II: Multiple-Ascending Dose-Escalation (Multiple Participant Cohorts)

[…]

In Part II dose-escalation, a minimum of 3 participants per cohort *will be enrolled who have a baseline sCEA level ≤20 ng/ml*. Participants within a cohort will be treated in a sequential manner with one week between the first and second participant, and at least one day between subsequent participants. However, if the first participant experiences a DLT within the first 7 days, then the time between the treatment of subsequent participants within the same cohort may be increased. The DLT evaluation window in Part II is defined as a period of 3 weeks after the first administration of RO7172508 in an IV Q3W schedule. Based on emerging data, the interval between dosing of each participant within a cohort or the DLT window may be adjusted if deemed appropriate by the Investigators and/or the Sponsor.

For each cohort, all participants will be followed through a 3-week DLT window (i.e., 21 days *after the first dose of RO7172508*). If fractionated dosing is implemented in Cycle 1 to improve tolerability, the DLT window will be extended to include the cycle where the planned target dose is administered in full i.e., *Cycle 1 Day 1 until* the end of Cycle 2. The DLT window will therefore be 6 weeks (42 days), or 8 weeks (56 days) if treatment has been delayed for no more than 14 days.

A new cohort can be opened when at least 3 evaluable participants of the previous cohort have completed the DLT window. *At least 3 evaluable participants must have a baseline sCEA level of ≤ 20 ng/ml.* If participants experience a DLT before completion of the last day of their DLT window, they will be considered as having completed their DLT window. Prior to opening a new cohort, the logistic regression model will be updated with the treatment outcome (i.e., the occurrence of DLT) and a new estimate of the MTD will be derived.

Enrollment into the next cohort will only resume after the Sponsor and the Investigators have jointly decided on the next dose-escalation step. Subject to clinical judgment, a new cohort of participants will be dosed at the new estimate of the MTD or the highest allowable dose based on pre-specified safety constraints as described below, whichever is lower and as guided by the mCRM-EWOC model. The design will continue as described, assigning participants to the MTD as estimated from all of the DLT data cumulatively, until one of the pre-defined stopping criteria is satisfied (see Section 4.1.4) or the pre-determined sample size of 60 DLT-evaluable participants is reached, whichever comes first. *Depending on emerging PK and safety data, the dose escalation may be evaluated taking into account sCEA levels at baseline in a sensitivity analysis (i.e. dose escalating more conservatively in case toxicity is associated with low baseline sCEA levels).*

[…]

- Dose-escalation to SC MTD

Once an MTD or OBD has been defined, or relevant clinical activity is seen (e.g., PR or better according to RECIST) for IV route of administration and schedule, SC administration will be tested. The starting dose *and regimen* for SC will be proposed based on the evaluation of the safety and efficacy data observed following IV administration; however, due to practical considerations, a minimum dose of 2 mg is defined for a single SC administration (Section 4.3).

In the *QW* cohorts, RO7172508 will be administered *three times per cycle (i.e.* QW*)*, with a maximum starting-dose of one third of the RO7172508 IV MTD dose or, in case MTD has not been reached, of the highest safe dose ≥ *6 mg* tested in the IV dose-escalation part. *For a Q3W regimen the starting dose will not exceed the highest safe dose tested in the IV Q3W dose escalation.*

The maximum allowed dose will be 160 mg QW *or 400 mg Q3W* (flat dose). Different dosing schedules (e.g., non-fractionated and/or fractionated dosing) may be tested.

[…]

The OBD (IV and SC) will be selected based on the overall clinical safety and activity, as well as available PK and PD data for RO7172508. *Data will be listed and summarized by* dose group as described in the analysis section (see Section 9.4).

Once a schedule, route of administration and OBD has been selected, and in case efficacy is observed during dose-escalation, disease-specific expansions may be opened to confirm these efficacy signals. The protocol will be amended in this case to describe treatment of these cohorts. *If one route of administration is not unequivocally superior, and a decision cannot be taken during or at the end of dose escalation, both routes of administration may be compared in disease specific expansions. Criteria for selection of a route of administration will then be added via the protocol amendment preceding the expansions, including endpoints.*

Section 4.1.3 *Obinutuzumab Pre-treatment*

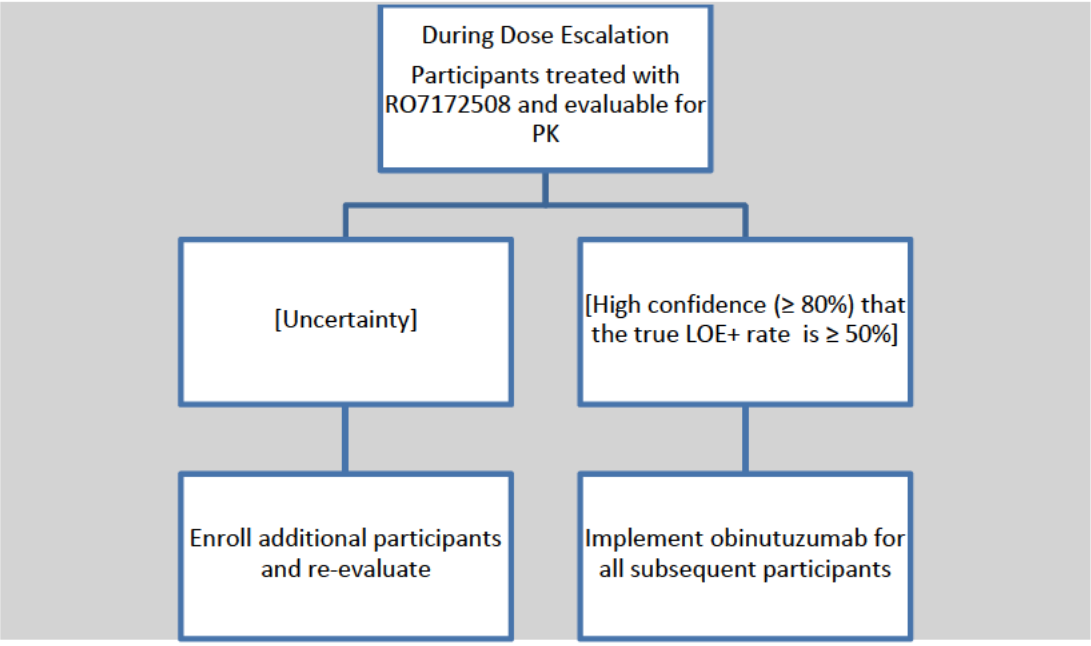
During the course of the study, the need for obinutuzumab pre-treatment will be assessed based on loss of RO7172508 exposure and/or ADA-related safety events. Previous experience with the combination of immunotherapy and obinutuzumab has shown the capacity of obinutuzumab to abrogate ADA formation, thereby maintaining exposure to the investigational compound as determined by PK analysis (see Section 2.2.2 and the RO7172508 investigator's brochure for further references).

During the course of the dose escalation, the decision to implement obinutuzumab will be based on a Bayesian posterior probability approach (see Appendix 8 for further details). At the time of the evaluation, if there is high confidence (80% confidence level) that the underlying true rate of participants with relevant loss of exposure is above 50% then obinutuzumab pre-treatment will be introduced for all subsequent participants in the study (see Section 6.1 and Appendix 8). If the criteria are not met, the dose escalation will proceed without obinutuzumab pre-treatment until the next assessment or the end of the dose escalation, whichever is reached first (see Appendix 8).

If obinutuzumab will be implemented during the course of the dose escalation, then the dose escalation will be run under the same condition as defined for Part II without obinutuzumab. The starting dose will be a dose that has been safely tolerated in Part II without obinutuzumab. Escalation, stopping rules and maximum number of participants applied to Part II will also apply to Part II with obinutuzumab pre-treatment.

The first assessment on the implementation of obinutuzumab will be conducted once PK data following 3 cycles of treatment are available from at least 14 participants across both Part I and II (see Appendix 8). Loss of exposure is defined as at least a 70% reduction in C_{max} at Cycle 3 from Cycle 1 in a participant. This threshold may be adapted based on emerging PK data. Ongoing assessments of safety and PK data will be performed for each cohort and at the end of dose escalation, to continuously evaluate the criteria for implementation of obinutuzumab pre-treatment. In addition, the incidence and titer of ADAs will be assessed on an ongoing basis throughout the study.

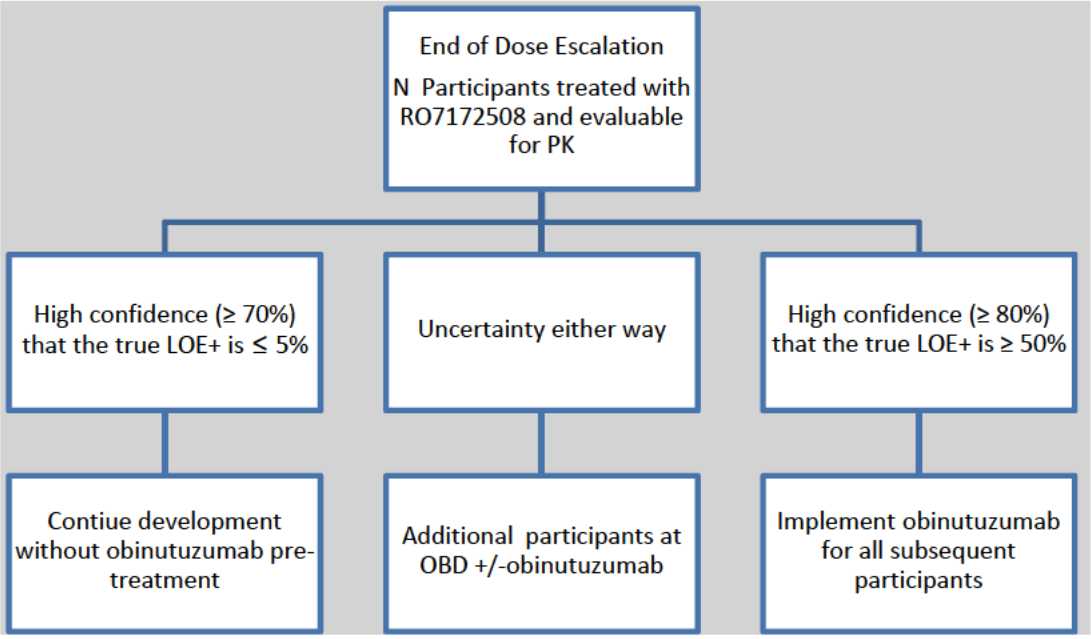
Figure 4 Decision Tree During Dose Escalation



If at the end of the dose escalation, the criteria to implement obinutuzumab pretreatment has not been met and at the same time, there is low confidence (i.e. <70% confidence level) that the true rate of loss of exposure is < 5%, then additional participants will be enrolled (see Appendix 8). Participants will then be randomized to cohorts at the OBD with or without obinutuzumab to further evaluate the safety and PK profile.

The need of obinutuzumab for further clinical development of RO7172508 will be determined based on the overall assessment of safety and PK data as well as pharmacodynamics effects.

Figure 5 Decision Tree at End of Dose Escalation



The total number of participants with relevant loss of exposure required to meet the criteria at subsequent evaluations, will depend on the actual number of participants enrolled and on the number of cohorts necessary to complete the dose escalation. For operating characteristics see Appendix 8.

Independent from loss of exposure, obinutuzumab pretreatment will be initiated if there is evidence of ADA-mediated hypersensitivity reactions or other safety signals that are likely related to ADAs. In such instance, obinutuzumab will be implemented for all subsequent participants and the enrollment of participants without obinutuzumab will be stopped.

Section 4.1.3.1 Dose-Limiting Toxicities

For the purpose of this study, a DLT will be defined as *any of the following events occurring during the DLT window and not attributable to underlying disease or intercurrent illness*~~any of the following events attributed to RO7172508 (i.e., related to RO7172508) and occurring during the DLT window~~:

[…]

Section 4.2.2 Rationale for Study Population

[…]

RO7172508 has the potential to bind to circulating sCEA, therefore, the exposure may be impacted following administration of low doses of RO7172508. A maximum baseline

sCEA level has been indicated *for doses < 12 mg* ~~in Part I and Part II (dose escalation)~~ to minimize the impact of RO7172508 binding to sCEA. *Preliminary PK data from the current study suggest sCEA may also impact the clearance of RO7172508. In order to further explore this relationship, at least 3 patients in each cohort in Part II should have a baseline sCEA level of ≤ 20 ng/mL.*

[…]

The recovery of RO7172508 at C_{max} was calculated using the above parameters for predicted doses < *12 mg* ~~in Part I and Part II (dose escalation)~~ (Figure 6).

[…]

Table 10 sCEA Concentrations Predicted to Result in 80% Recovery of RO7172508 at ~~Part I~~ Doses *Less Than 12 mg*

Dose (μg)	*65*	*160*	*400*	*800*	*1600*
sCEA concentration (ng/mL)	*22-24*	*28-31*	*44-49*	*70-78*	*123-137*
Dose *(mg)* ~~(μg)~~	*3.2*~~65~~	*6.4*~~160~~	*12*~~400~~	~~800~~	~~1600~~
sCEA concentration (ng/mL)	*229-254*~~22-24~~	*440-489*~~28-31~~	*809-899*~~44-49~~	~~70-78~~	~~123-137~~

Section 4.3.1 RO7172508

[…]

A maximum dose of 400 mg *Q3W* of RO7172508 has been defined. The C_{max} observed at Cycle 1 of 400 mg (MTD) *cibisatamab* ~~RO6958688~~ was 113 μg/mL. Assuming a potency factor of 20, an equivalent RO7172508 C_{max} of 5.6 μg/mL is estimated to be achieved by 25 mg. The clinical potency may differ from the in vitro levels*;* therefore, a maximum dose of 400 mg has been defined to allow this to be tested. The dose-escalation will only take place once a full evaluation of safety data has taken place and the dose-increment levels may be reduced to ensure the participant's safety. Dose-fractionation may also be implemented in Cycle 1 where a dose not exceeding 400 mg will be administered over one cycle e.g., 40 mg on Day 1, 120 mg on Day 8 and 240 mg on Day 15. The maximum SC dose administered QW will be 160 mg QW which is 480 mg over a three-*-*week period*/cycle*. By applying a conservative bioavailability of ~80% this would equate to 400 mg Q3W IV.

Section 4.3.2 *Obinutuzumab*

If required, during the course of this study, based on the incidence of ADA-induced loss of exposure or safety events, obinutuzumab will be administered as detailed in the SoA (Section 1.3). Obinutuzumab will be administered as pre-treatment for RO7172508 either as 2000 mg of obinutuzumab IV on one day (Day -7) or as 1000 mg of obinutuzumab IV on 2 consecutive days (Day -7 and Day -6) as specified in the SoA as per the site's choice. Details regarding the infusion process are provided in Section 6.1. ADA titers and PK of both RO7172508 and obinutuzumab will be monitored as described in Section 4.1.3.

The interval between obinutuzumab and the start of treatment has been determined based on Study BP39365, which is exploring the clinical activity of RO6874281 (FAP-IL2v) in combination with atezolizumab. Five patients were pretreated with obinutuzumab 7 days prior to the combination treatment. It could be confirmed that complete B cell depletion was observed at the start of the combination treatment seven days after obinutuzumab was administered. There was no evidence of ADA formation in these participants when assessing ADA titers for RO6874281 (FAP-IL2v) and atezolizumab (RO5541267) up to 32 weeks of treatment. One patient showed positive ADA titers after 32 weeks of RO6874281/atezolizumab combination, which correlated with the reconstitution of B cells. Another patient remains on study after 52 weeks with no evidence of ADA titers and B cells remain depleted. Without obinutuzumab pretreatment in Study BP39365, the incidence of ADAs is approximately 80%. The kinetics of B-cell depletion and repletion have also been studied in Study BO20999 and following the administration of obinutuzumab a rapid depletion of B-cells was observed by Study Day 8 in CLL patients (first measurement after administration).

Further details are provided in the obinutuzumab Investigator's Brochure.

Section 5 Study Population

[…]

In Part I, approximately 5 participants will be enrolled. In Part II, *up to* approximately ~~60~~ *75* participants during each dose-escalation*, including additional 15 participants* (1*5*~~2~~0 participants total in both IV and SC) will be enrolled (Section 9.2). *In case the OBD is evaluated with and without obinutuzumab, an additional 15 participants may be enrolled.*

Section 5.1 Inclusion Criteria

[…]

4. For ~~Part I (single participant cohorts) and Part II (dose escalation)~~ <*12 mg dose* cohorts, serum CEA (sCEA) levels below a certain threshold is required as follows:

    - For dose cohorts 65-159 μg, a*n* sCEA level of < 22 ng/mL.
    - For dose cohorts 160-399 μg, a*n* sCEA level of < 28 ng/mL.
    - For dose cohorts 400-799 μg, a*n* sCEA level of < 44 ng/mL.
    - For dose cohorts 800-1599 μg, a*n* sCEA level of < 70 ng/mL.
    - For the dose cohort of 1.6 - 3.1 mg, a*n* sCEA level of < 123 ng/mL.
    - *For the dose cohort of 3.2 - 6.3 mg, an sCEA level of < 229 ng/mL.*
    - *For the dose cohort of 6.4 -11.9 mg, an sCEA level of < 440 ng/mL.*

    If dose fractionation is implemented, the sCEA threshold for inclusion should correspond to the dose range of the first dose administered.

    For Part II, at least 3 participants in each cohort should have a baseline sCEA level ≤ 20 ng/mL.

5. **For Part II**, participants with locally advanced and/or metastatic solid tumor expressing cytoplasmic and/or membranous high-CEA or moderate/low-CEA on archival material (or fresh biopsy when archival is not available), who have progressed on a SOC therapy, are intolerant to SOC, and/or are non-amenable to SOC. Participants must have a lesion amenable to biopsy (except participants with NSCLC, which may be enrolled with archival tissue available only). *For participants with colorectal cancer (CRC) only, the CEA assessment by IHC should be performed but the result is not required to enroll the participant.*

    - High-CEA: ≥ 20% of tumor cells with IHC 2+ and/or 3+.
    - *L***~~Moderate/l~~ow-CEA:** ~~< 20%~~ *≥ 20% of tumor cells with the sum of any IHC intensity (1+ 2+ and 3+) and not considered CEA-High*~~of tumor cells with IHC 2+ and/or 3+ and/or ≥ 20% of tumor cells with IHC 1+.~~

[…]

11. Adequate liver function: total bilirubin ≤ 1.5 × the upper limit of normal (ULN; excluding Gilbert's Syndrome), *aspartate aminotransferase (*AST*)* and/or *alanine aminotransferase (*ALT*)* ≤ 2.5 × ULN (in case of liver metastases, ≤ 5 × ULN).

[…]

15. Male and female participants

[…]

b) Male Participants

During the treatment period and for at least 2 months after the last dose of study treatment~~}~~, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom ~~plus an additional~~*or a* contraceptive method that ~~together~~ result in a failure rate of < 1% per year, with partners who are WOCBP (as defined in Section 1 of Appendix 5).

[…]

Section 5.2 Exclusion Criteria

[…]

12. Presence of <u>bilateral</u> lung lesions with either > 3 lesions per lung or ≥ 1 lesion per lung with a diameter > 3 cm *(only unequivocal lesions of >1 cm are to be counted for this criterion, unless there is miliary metastatic-type diffuse disease, then these participants are ineligible).*

[…]

~~19.~~ Other Exclusions

19. Known hypersensitivity to any of the components of RO7172508.

Specific Exclusion Criteria if Pre-treatment with Obinutuzumab is Implemented

20. Known HIV (HIV testing will be performed at screening if required by local regulations)

21. Positive test results for chronic HBV infection (defined as positive HBsAg serology), HBcAb indicating an active viral infection and positive test results for HCV (HCV antibody serology testing).

22. Participants positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV ribonucleic acid (RNA).

23. History of progressive multifocal leukoencephalopathy.

24. Active TB requiring treatment within 3 years prior to baseline.

25. Latent TB diagnosed during Screening.

26. Positive test results for human T-lymphotropic virus 1 (HTLV 1).

27. *HTLV testing is required in participants from endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia)*
28. *Known hypersensitivity to any of the components of obinutuzumab.*

Section 6 Treatments

[…]

The investigational medicinal products (IMP) required for completion of this study (RO7172508*, obinutuzumab* and tocilizumab) will be provided by the Sponsor. Administration of study treatment will be at the study centers under supervision of qualified site staff.

Section 6.1 Treatments Administered

[…]

Administration of Obinutuzumab

The obinutuzumab Drug Product will be supplied by the Sponsor as a 50 mL single dose glass vial containing 1000-mg liquid concentrate in 40 mL (25 mg/mL) for infusion. In addition to the drug substance, the liquid is also composed of histidine/histidine-HCl, trehalose and poloxamer 188 (see Table 12).

Obinutuzumab will be administered either as a single dose of 2000 mg 7 days (D-7) before the first dose of RO7172508 (C1D1) or two doses of 1000 mg over days 6 and 7 days (D-6 and D-7) before the first dose of RO7172508 (C1D1).

For information on the formulation and handling of obinutuzumab, refer to the pharmacy manual and Obinutuzumab Investigator's Brochure.

Table 12 Obinutuzumab Summary of Treatment Administered

Study Treatment Name	*Obinutuzumab*
Dosage Formulation	*Concentrate for solution for IV infusion*
Unit Dose Strength(s)/Dosage Level(s)	*25 mg/mL*
Dose	*2000 mg or split doses of 2x 1000 mg*
Route of Administration	*IV*
Dosing Instructions	*see Pharmacy Manual*
Packaging and Labeling	*Study treatment will be provided in a carton (one labeled vial per box). Each carton will be labeled as required per country requirement.*

Section 6.1.1 Pre-medication

[…]

In the event that the change in the route of administration from IV to SC does not mitigate the tumor inflammatory events or IRRs, then the same steroid regimen may be implemented as described in Table 14 and Table 15. These regimens are based on the expected duration of inflammatory events and they may be reduced or modified based on emerging data. *Also, they may be extended from Cycle 1 to subsequent cycles, in case tumor inflammation and/or IRR occur at later cycles.* Pre-medication may also include 1000 ml saline, 50 mg indomethacin (or equivalent non-steroidal anti-inflammatory [NSAID]), ~~10 mg metoclopramide (or equivalent anti-emetic)~~ and 50 mg diphenhydramine (or equivalent H1 antagonist).

Table 14 Steroid Use on Cycle 1 of RO7172508 Infusion to be implemented in the event of frequent IRR/CRS *or gastrointestinal RO7172508-related toxicity* occurrence after first administration

Timing	Dose
~~C1D -1: 12-24 hours before RO7172508 infusion~~	~~1 mg/kg prednisone IV/PO~~
C1D1: ~~up to 60 minutes~~ *4 to 6 hours* before RO7172508 infusion	~~0.5~~*1* mg/kg *methylprednisolone*~~methyl-prednisone~~ IV*~~/PO~~ 1 g paracetamol PO TID 2 mg loperamide PO
C1D1: approximately 2 hours after RO7172508 infusion	*1 mg/kg prednisone IV/PO**
C1D2: approximately 24 hours post-RO7172508 EOI	~~0.5~~*1* mg/kg prednisone IV/PO* 1 g paracetamol PO TID 2 mg loperamide PO**
C1D3: approximately 48 hours post-RO7172508 EOI	0.5 mg/kg prednisone IV/PO* 1 g paracetamol PO TID
C1D4: approximately 72 hours post-RO7172508 EOI	0.5 mg/kg prednisone IV/PO* 1 g paracetamol PO TID

C: Cycle; D: Day; EOI: end of infusion; IV: intravenous; PO: oral; TID: 3 times a day.

** rounded up to next multiple of 10 mg (or equivalent doses of mid acting steroids)*

*** subsequent treatment with loperamide only to be given as clinically indicated*

Table 15 Steroid Use on Cycle 1 of RO7172508 *or gastrointestinal RO7172508-related toxicity* to be implemented in the event of frequent IRR/CRS persisting despite dose fractionation

Timing	Dose
~~C1D 1: 12 24 hours before RO7172508 infusion~~	~~0.5 mg/kg prednisone IV/PO~~
C1D1: ~~up to 60 minutes~~ *4 to 6 hours* before RO7172508 infusion	~~0.5~~*1* mg/kg *methylprednisolone*~~methyl prednisone~~ IV*/~~PO~~ 1 g paracetamol PO TID 2 mg loperamide PO
CD1D1: approximately 2 hours post-RO7172508 EOI	~~0.5~~ *1* mg/kg prednisone IV/PO 1 g paracetamol PO TID
C1D2~~7~~: *approximately* ~~12~~ 24 hours ~~before~~ *post-*RO7172508 *EOI* ~~infusion~~	~~0.5~~*1* mg/kg prednisone IV/PO
C1D8: ~~up to~~ 60 minutes before RO7172508 infusion	~~0.5~~*1* mg/kg *methylprednisolone*~~methyl prednisone~~ IV*/~~PO~~ 1 g paracetamol PO TID 2 mg loperamide PO**
C1D8~~9~~: *approximately 2 hours post-RO7172508* ~~infusion~~*EOI*	0.5 mg/kg prednisone IV/PO 1 g paracetamol PO TID
C1D9~~14~~: ~~12~~ *approximately* 24 hours ~~before~~ *post-*RO7172508 *EOI* ~~infusion~~	0.5 mg/kg prednisone IV/PO
C1D15: ~~up to~~ 60 minutes before RO7172508 infusion	~~0.5~~*1* mg/kg *methylprednisolone*~~methyl prednisone~~ IV*/~~PO~~ 1 g paracetamol PO TID 2 mg loperamide PO **
C1D15~~6~~: *approximately 2 hours* post-RO7172508 EOI	~~0.5~~*1* mg/kg prednisone IV/PO 1 g paracetamol PO TID
C1D16: approximately 24 hours post-RO7172508 EOI	*0.5 mg/kg prednisone IV/PO*

C: Cycle; D: Day; EOI: end of infusion; IV: intravenous; PO: oral; TID: 3 times a day.

** rounded up to next multiple of 10 mg (or equivalent doses of mid acting steroids)*

*** subsequent treatment with loperamide only to be given as clinically indicated*

In addition to the above mentioned premedication regimens, additional premedication may be implemented after agreement between Sponsor and Investigators for prophylaxis of RO7172508-related toxicity at cycle 1 and/or at subsequent cycles:

- *From 30 to 60 minutes before administration of RO7172508, 5-HT3-receptor antagonist administration (preferably a long acting antagonist such as palonosetron 500 µg);*
- *Budesonide 9mg daily to start 3 days before first RO7172508 and to be continued up to 7 days after first RO7172508 administration.*

Subsequent RO7172508 Infusions

Participants who experienced a Grade 2 IRR *or other RO7172508-related toxicity within 24 hours of RO7172508 administration* on a previous infusion should be pre-medicated for subsequent infusions. *The regimen indicated in Table 14 will be recommended for subsequent cycles, however in lieu of IV methylprednisolone administration, an equal oral dose of methylprednisolone (or equivalent) can be used. Similarly, the additional premedication regimens may be moved to subsequent cycles to prevent recurrence of the toxicity that occurred in Cycle 1. Premedication regimens for subsequent cycles may be reduced or omitted in case of ≤ Grade 1 events in the previous cycle.*

- ~~Paracetamol (500-1000 mg oral [PO] or IV) and diphenhydramine (25-50 mg PO or IV; or an alternative histamine $H_{1/2}$ antagonist at an adequate dose). If a participant experienced a Grade 3 IRR, the same will apply in addition to corticosteroid 200 mg hydrocortisone IV (or equivalent dose of another corticosteroid).~~

[…]

For participants who experience an IRR-like reaction with a single and isolated symptom, such as fever that occurs within 24 hours after the study treatment infusion was completed, the use of pre-medication such as paracetamol, anti-histamine, and corticosteroids is not foreseen prior to subsequent RO7172508 administrations. The event will be reported as a single AE (e.g., fever). Pre-medication with corticosteroids of those participants at subsequent infusions needs approval from the Sponsor and the treatment and management at the time of an event is at the discretion of the Investigator. Pre-medication may be changed based on emerging data *and the regimens described above should be considered as the maximum suggested regimens. After collecting information on the effectiveness of the above mentioned premedication regimens scheduling and dose intensities may be reduced but not increased.*

Premedication Prior to Obinutuzumab Administration

The use of corticosteroids, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and/or antihistamines is required to minimize expected IRR reactions associated with the administration of obinutuzumab. Pre-medication must be administered prior to obinutuzumab administration. A list of the mandatory pre-medications is provided in Table 16.

Hypotension may occur as a result of an IRR adverse event. Therefore, it is recommended that antihypertensive drugs not be given on the morning of, and throughout the infusion of obinutuzumab, even if clinically indicated. Patients with a history of cardiac disease should be monitored closely.

Table 16 Premedication Requirements for Obinutuzumab

Pre-Medication	*Timing of Administration*
Prednisolone 100 mg administered by IV infusion (or equivalent)	*At least 60 minutes prior to the obinutuzumab infusion*
Analgesic/anti-pyretic (e.g., paracetamol/oral acetaminophen 500 –1000 mg) administered orally or by IV infusion	*At least 30 minutes prior to the obinutuzumab infusion*
Antihistamine (e.g., oral diphenhydramine 50 –100 mg) administered orally or by IV infusion (or an alternative anti-histamine at an adequate dose)	*At least 60 minutes prior to the obinutuzumab infusion*

Section 6.6 Dosage Modification

[…]

If a participant experiences obinutuzumab-related toxicity on Day -7 that requires the subsequent administration of obinutuzumab on Day -6 to be delayed, administration of obinutuzumab up to Day -5 is acceptable. Any obinutuzumab-related toxicity should resolve to NCI CTCAE Grade ≤ 2 for hematological toxicities or ≤ 1 for non-hematological toxicities before RO7172508 administration. The first RO7172508 administration can be delayed for of up to 1 week and if toxicity persists, the start of RO7172508 treatment will need to be agreed with the Medical Monitor.

Section 8.1.1 Tumor and Response Evaluations

[…]

The data collected for RECIST v1.1 *(Appendix 6)* ~~and mRECIST~~ will be used by the Sponsor to calculate programmatically 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 cancer immunotherapy field (Seymour et al 2017).

Section 8.2 Safety Assessments

Planned time-points for all safety assessments are provided in the SoA (Section 1.3). *In order to better understand related adverse events, if any unscheduled assessments are performed during the study as part of standard of care, such as biopsies at the time of inflammation, these samples and/or results can be shared with the Sponsor for further analysis.*

Section 8.3.8 Management of Specific Adverse Events

Guidelines for the management of participants who experience specific AEs to the IMPs other than RO7172508 (obinutuzumab and tocilizumab) are provided in the obinutuzumab and tocilizumab Investigator's Brochure and local prescribing information. Guidelines for the management of participants who experience AEs associated with RO7172508 are provided in Table 17, Table 18, and Table 19. For cases in which management guidelines are not covered in this protocol or in the obinutuzumab/tocilizumab Investigator's Brochure and local prescribing information, toxicities should be treated as deemed appropriate by the Investigator according to best medical judgment and local medical guidelines. Please see the RO7172508 Investigator's Brochure for ~~the~~ *further* detail*s of the safety profile*~~s of the management of specific AEs~~.

Section 8.3.8.1 Infusion-Related Reactions/Cytokine Release Syndrome

Administration of RO7172508 may cause a spectrum of infusion-related adverse events that typically occur during, shortly after, or within 24 hours after the infusion and could be associated with an IRR or CRS.

IRRs are typically seen with the first two cycles and without symptoms of hypoxia and/or hypotension. In contrast, CRS is more likely to occur with the symptoms of hypoxia and/or hypotension at any cycle and with any symptom following from the third cycle onward. IRR events are therefore defined as taking place in association with the first two infusions and without symptoms of hypotension and/or hypoxia.

Given the overlap in signs and symptoms, IRRs may be indistinguishable from CRS, defined as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, shortness of breath, and renal, coagulation, hepatic, and neurologic disorders (Lee et al. 2014). Severe CRS may be associated with other clinical sequelae, such as disseminated intravascular coagulation and capillary leak syndrome.

Given that IRRs may be indistinguishable from CRS based on symptomatology, single-treatment management guidelines are being recommended for both IRRs and CRS, during or up to 24 hours after infusion of RO7172508. The approach to have single-treatment management guidelines for IRR and CRS will continue to be reviewed as additional safety data accumulate.

Table 17 provides guidelines for management of infusion-related reactions/ cytokine release syndrome.

Table 17 Recommendations for Management of IRRs and CRS considered related to RO7172508[a]

Symptoms	Guidance
Grade 1 Fever, constitutional symptoms	– If RO7172508 infusion is ongoing, slow infusion to ≤50% or interrupt infusion – Symptomatic treatment and supportive care – *Monitor fluid balance and administer IV fluids as clinically indicated* – At next cycle administer pre-medications that may include antihistamine, antipyretics/NSAIDS, antiemetic, and corticosteroids (See Table 14 *and* Table 15 ~~&~~)
Grade 2 Hypotension: responds to fluids OR Hypoxia*: requires <40% FiO_2 (or ≤5 L/min of 100% O2) to maintain adequate hemoglobin oxygen saturation	– Follow all Grade 1 recommendations – Hold further RO7172508 treatment until symptoms completely resolved – *At the restart of the infusion,* ~~S~~slow down the rate of infusion to 25% of original rate – If event occurred during infusion, and symptoms recur with the same or greater severity following interruption of RO7172508 infusion, the infusion must be stopped immediately. *Consider to manage as a Grade 3 event.* No further RO7172508 will be administered for the cycle~~; if hypotension or hypoxia recurs manage as grade 3 event~~ – Monitor cardiac and other organ functions closely – Hemodynamic support as indicated and oxygen for hypoxia – Admit to ICU as appropriate – *Consider administering a single dose of tocilizumab IV 8 mg/kg* – If no improvement within 24 hours: **a)** Notify Medical Monitor **b)** Administer IV corticosteroids (e.g., methylprednisolone [2 mg/kg/day] or dexamethasone 10 mg if neurologic symptoms are present) – Additional monitoring and evaluation: – Consider 24 hour hospitalization – Work up for organ functions (e.g. liver, cardiac) based on clinical assessment of the Investigator – May receive RO7172508 in next cycle if symptoms resolve to Grade ≤1 with the approval of the Medical Monitor including considerations for dose reduction and/or reduction of infusion rate at the next administration. – At next cycle administer pre-medications that may include antihistamine, antipyretics/NSAIDS, antiemetic, and corticosteroids
Grade 3 Hypotension: requires vasopressor support OR Hypoxia*: requires >40% FiO_2 or >5 L/min O2 to maintain adequate hemoglobin oxygen saturation	– If RO7172508 infusion is ongoing, stop infusion immediately – No further RO7172508 will be administered for the cycle – Cardiopulmonary and organ function monitoring in ICU – Closely monitor and maintain fluid balance; and other supportive care as clinically indicated – Vasopressor support for hypotension with high and repeated doses if required – Notify Medical Monitor – Initiate IV corticosteroids (e.g., methylprednisolone [2 mg/kg/day] or dexamethasone 10 mg if neurologic symptoms are present) – Administer tocilizumab 8 mg/kg IV – If no clinical improvement within 24 h: repeat dose of tocilizumab 8 mg/kg – Additional monitoring and evaluation: – Hospitalize patient for 24 hours

Symptoms	Guidance
	– Work up for organ functions (e.g. liver, cardiac) based on clinical assessment of the Investigator
	– Permanently discontinue RO7172508 *and follow the Schedule of Assessments (*Table 5)
Grade 4	– Follow all Grade 3 guidelines
Hypoxia: Mechanical ventilation required	– Permanently discontinue RO7172508

[a] Grading of events is based on CTCAE V5.0

* Isolated hypoxia (without hemodynamic instability) requiring oxygen support in a patient with tumor (primary or metastatic) in the lung should be managed as per tumor inflammation guidelines (Table 18) and not per CRS guidelines (Table 17).

Section 8.3.8.2 Suspected Tumor Inflammation

Adverse events associated with tumor inflammation have been reported with T-cell engaging therapies and are consistent with the mechanism of action of such therapies that lead to influx of T-cells into tumor sites. Tumor inflammation is driven by influx of T cells and it is dependent on the mechanism of action of RO7172508. Along with the volume increase dependent on the influx of T cells, there may be an additional volumetric component possibly dependent by local inflammation. Events involving tumor inflammation, including tumor flare, have been reported in studies with in-class agent cibisatamab~~RO6958688~~. These events tend to occur with a short time to onset following administration and may present with varying degrees of severity.

In addition, depending on tumor size and anatomic location, events associated with tumor inflammation may potentially result in mass effects on vital structures, including airways, major blood vessels, and/or major organs. Depending on the nature of the tumor inflammation, further medical and/or surgical management may be necessary (e.g. anti-inflammatory agents, airway management, decompression, cardiac function monitoring in terms of ejection fraction). Participants with tumors involving critical anatomic locations should be closely monitored for tumor inflammation and prospective consideration for preventive or interventional measures may need to be considered or planned prior to dosing. The treating physician/study investigator should contact the Medical Monitor to discuss risk assessment and mitigation strategies prior to initiating RO7172508 treatment in case participants present disease closed to vital structures.

For further safety information, refer to the RO7172508 Investigator Brochure.

[…]

Table 18 Management of Suspected Tumor Inflammation

Event	Initial Management Recommendation	Action to be Taken with RO7172508
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 Grade4	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 organs systems ~~(e.g., colitis, enteritis, increased liver enzymes)~~		
Grade 1 or 2	Monitor participant closely	Continue if Grade 1 event (for Grade 2 events, 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 permanent discontinuation (including liver enzyme elevations).*~~Hold until resolution to Grade ≤ 1~~*.Exceptions may be warranted after discussion of benefit/risk profile of a specific patient 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.	~~Consider permanent discontinuation after discussion with Medical Monitor.~~

Section 8.3.8.3 Management of Diarrhea*/Colitis*

[…]

Table 19 Management of Diarrhea/*C*olitis

Event	Management Recommendations
Grade 1	• Continue treatment with RO7172508. • Initiate anti-diarrheal treatment (e.g., loperamide) as soon as possible. • Monitor the participant closely. • Ensure appropriate fluid intake. • If symptoms persist despite optimal anti-diarrheal treatment for more than 5 days, perform gastrointestinal (GI) work up*.
Grade 2	• Withhold treatment with RO7172508. • Initiate anti-diarrheal treatment (e.g., loperamide) as soon as possible • Monitor the participant closely, perform GI work up*. • Ensure appropriate fluid intake • If symptoms do not improve to Grade ≤1 despite optimal anti-diarrheal treatment within 2 days, consider treatment with IV or oral corticosteroids (1mg/kg/day oral prednisolone or equivalent). • If diarrhea does not improve after 48 hours of corticosteroid treatment of 1mg/kg/day, increase dose to 2mg/kg/day. • If symptoms do not resolve despite corticosteroid treatment, consider referring the participant to GI specialist • RO7172508 can be re-started if symptoms resolve to Grade ≤ 1.
Grade 3	• Withhold treatment with RO7172508. • Refer the participant to GI specialist for diagnostic procedures (stool culture, endoscopy) and appropriate treatment. • Initiate corticosteroid treatment IV (2mg/kg/day IV methylprednisolone or equivalent). • Ensure appropriate fluid intake. • RO7172508 can be re-started if symptoms resolve to Grade ≤ 1. • *If no improvement after 24 hours, consider treatment as per Grade 4 guidelines*
Grade 4	• Permanently discontinue treatment with RO7172508. • Refer the participant to GI specialist for diagnostic procedures (stool culture, endoscopy) and appropriate treatment. • Manage all symptoms by aggressive symptomatic treatment. • Initiate corticosteroid treatment IV. • If the there is no improvement for more than 48 hours, immunosuppressive treatment might be considered (such as infliximab).

* GI work up *for further evaluation (e.g. endoscopy) and* includes stool culture ~~(in case of positive results e.g., Clostridium difficile, enteric bacteria, cytomegalovirus treat with antibiotics if appropriate). If the results of stool culture are negative, consider referring the participant to GI specialist for further evaluation (endoscopy).~~

Section 8.3.8.4 *Management of Immunogenicity*

Administration of therapeutic antibodies may cause the formation of ADAs and immunogenicity is a potential risk for RO7172508. There is currently no evidence of ADAs in participants treated with RO7172508, with the limitation that only a low number of participants have been exposed. However, severe AEs (including two fatal events) associated with ADA formation were observed during clinical development of in class agent cibisatamab.

All participants will be monitored at regular intervals for the development of ADAs against RO7172508 (see Section 8.5.1 for details). In case of emergence of AEs (in particular hypersensitivity reactions and CRS) possibly related to the development of ADAs against RO7172508, management will follow guidelines as summarized in Table 17. In all cases of AEs associated with the development of ADAs, treatment discontinuation should be immediately considered even if the event is low grade after discussion with Medical Monitor.

As an additional mitigation strategy, obinutuzumab pre-treatment will be initiated if there is evidence of ADA mediated hypersensitivity reactions or other safety signals that are likely related to ADAs (see Section 4.1.3 for details). In such instance, obinutuzumab will be implemented for all subsequent participants and the enrollment of participants without obinutuzumab will be stopped.

Section 8.5 Pharmacokinetics

Serum samples will be collected for *RO7172508* PK analyses for both IV and SC administrations.

[…]

Serum samples will be collected for obinutuzumab PK analyses in those participants who receive obinutuzumab as pre-treatment.

Section 8.5.1 Immunogenicity Assessments

[…]

Antibodies to RO7172508 will be evaluated in blood samples collected from all participants according to the SoA (Section 1.3). Additional ADA samples should also be collected at the time of treatment discontinuation or at the safety follow-up visit ~~and in participants who experience a Grade ≥3 IRR and in participants with clinical signs of hypersensitivity reaction, in particular immune complex reaction~~. In each case, for each collected ADA sample, a corresponding PK sample will be collected at the same time-point for the determination of the RO7172508 concentration. *Participants experiencing a Grade ≥3 toxicity potentially related to ADAs will not be further treated with RO7172508 (see Section 7.1).*

[…]

Antibodies to obinutuzumab will be evaluated in all participants who receive obinutuzumab as pre-treatment according to the SoA.

Section 8.6 Pharmacodynamics

[…]

- **Serum and/or plasma samples:** PD biomarkers such as cytokines and inflammation markers (including but not limited to TNFα, IFNγ, IL-6, *Macrophage Inflammatory Protein [*MIP*]*, etc.) will be analyzed. Because these measurements are also safety measure assessments during any IRRs, they will be examined in participants enrolled in both Part I and Part II of the study. Disease-monitoring markers that include but are not limited to sCEA will also be assessed.
- **Archival tissue and fresh tumor biopsy:** ~~If archival is not available, fresh biopsy collected at baseline will be used.~~ Study enrollment will be based on CEA status assessed on archival tissue (*with the exception of participants with CRC).* ~~I~~If archival is not available, fresh biopsy collected at baseline will be used~~)~~. Mandatory tumor biopsy samples obtained in Part II *for all participants (including participants with CRC)* at baseline and on-treatment (Cycle 2 Day 8; see SoA, Section 1.3) will be assessed for changes in immune cell numbers and activation characteristics as well as changes in tumor markers such as PD-L1. These analyses will be performed by flow cytometry, molecular and/or immunohistochemistry methods with respect to changes in the characteristics of lineage (CD4+ T-cells, CD8+ T-cells, NK cells, monocytes, T-regulatory cells, and B-cells), activation (including but not limited to CD25, CD69, etc.), differentiation (including but not limited to Ki67, PD1, TIM3, ICOS, etc.), and TCR Vβ repertoire.

Whole blood, serum/plasma, and tissue samples will be collected at time-points specified in the SoA (Section 1.3) *and may be modified or reduced based on emerging data. The number of samples will not exceed what is described in the SoA.*

Section 8.8 Biomarkers

[…]

~~In particular, a~~*A*rchival tumor tissue is to be obtained from all participants, if available, in order to perform CEA assessment for participant eligibility *except for participants with CRC* (refer to the Laboratory Manual). Both archival and fresh tumor biopsy specimens will be analyzed with respect to changes as described (Section 8.6) including but not limited to immune and tumor cell characteristics, TCR Vβ repertoire etc.

Section 9.2 Sample Size Determination

Part I will enroll up to approximately 5 participants. The sample size is determined by the dose-increment steps implemented in this part.

In Part II, it is anticipated that a maximum of approximately 60 ~~evaluable~~ participants will be enrolled in each dose-escalation phase (IV and SC) (up to approximately 75 participants if one or several cohorts are expanded). *In case the OBD dose cohort is expanded both with and without obinutuzumab, an additional 15 participants may be enrolled.*

The probability of observing at least one event out of 15 participants for a true underline rate of 10% is 79% while out of 5 patients is 41%. Probabilities of the occurrence of 1 or more events for different ranges of true underline rates and different participant numbers are summarized in Table 20.

The exact sample size for the dose-escalation part cannot be pre-determined and depends on the number of cohorts needed to reach the MTD (or highest safe dose if MTD is not reached).

Table 20 Probabilities for Observing Adverse Events

Total N of Participants	*True AE Probability*	*Probability that AE ≥ 1*	*Probability that AE ≥ 2*	*Probability that AE ≥ 3*
15	*0.1*	*0.79*	*0.45*	*0.18*
	0.2	*0.96*	*0.83*	*0.60*
	0.3	*1.00*	*0.96*	*0.87*
	0.4	*1.00*	*0.99*	*0.97*
	0.5	*1.00*	*1.00*	*1.00*
10	*0.1*	*0.65*	*0.26*	*0.07*
	0.2	*0.89*	*0.62*	*0.32*
	0.3	*0.97*	*0.85*	*0.62*
	0.4	*0.99*	*0.95*	*0.83*
	0.5	*1.00*	*0.99*	*0.95*
5	*0.1*	*0.41*	*0.08*	*0.01*
	0.2	*0.67*	*0.26*	*0.06*
	0.3	*0.83*	*0.47*	*0.16*
	0.4	*0.92*	*0.66*	*0.32*
	0.5	*0.97*	*0.81*	*0.50*

Section 9.3 Populations for Analyses

Table 21 Analysis Populations

Population	Description
Efficacy	All participants who received at least one dose of RO7172508.
Safety	All participants enrolled in the study who received at least one dose of study treatment *(RO7172508 and/or obinutuzumab if applicable)* will be included in the safety population. Unless otherwise specified, the safety population will be the default analysis set used for all analyses.

[…]

Section 9.4 Statistical Analyses

The data will be analyzed by the Sponsor and/or designated Contract Research Organization (CRO). Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and biomarker measurements. Data will be summarized by cohort and regimen within each part and CEA level where applicable*,~~.~~ including the additional participants that may be enrolled in expanded cohorts (see Section 4.1.2.2). Participants who receive only obinutuzumab but no dose of RO7172508 will be summarized separately.*

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment *(RO7172508 or obinutuzumab (if applicable) as appropriate)*.

The following endpoints may be used to select a route of administration for further development: PD parameters including T-cell activation in blood and in the tumor; pharmacokinetic parameters such as AUC, C_{max} and half-life; tolerability and safety; as well as incidence of ADAs and their effect on exposure. Clinical efficacy will be considered, but is not expected to be a key criterion, as efficacy will likely be affected by parameters which cannot be controlled for in such small cohorts. Data will be listed and summarized by dose group as described in this analysis section. Analyses are exploratory in nature and no formal hypothesis testing will be performed.

If one route of administration is not unequivocally superior, and a decision cannot be taken during or at the end of dose escalation, both routes of administration will be compared in disease specific expansion. Criteria for selection of a route of administration will then be added via the amendment preceding the expansions, including endpoints.

Section 9.4.2 Efficacy Analyses

[…]

- ORR and DCR are both determined as the rate of participants with an observed tumor response of CR or PR (ORR) or CR, PR or SD (DCR). ORR and DCR will be derived for ~~both~~ RECIST v1.1 ~~and mRECIST~~.

Section 9.4.3 Safety Analyses

Unless otherwise specified, the safety population will be the default analysis set used for all analyses. *Those participants who receive only obinutuzumab, but withdraw from the study before receiving RO7172508, will be summarized separately.*

DLT evaluable participants will be used in the determination of the MTD.

The safety endpoints and appropriate analyses are summarized in Table 23.

Table 23 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. 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 Section 3.1 of Appendix 2. AEs will be summarized by mapped term and appropriate thesaurus level. Toxicity grade, seriousness and relationship to study treatment will be presented, as well as *listings* of deaths, AEs leading to death and premature withdrawal from study treatment. Glossary of AEs, medication and procedures will be provided. *AE occurring between obinutuzumab pre-treatment (if applicable) and the first administration of RO7172508 will be summarized separately.*

Section 9.4.4 Pharmacokinetic Analyses

[…]

Individual and mean serum obinutuzumab concentration versus time data will be tabulated.

Section 9.4.5 Immunogenicity Analyses

[…]

Antibodies to obinutuzumab will be evaluated in blood samples using appropriate assays from all participants who receive obinutuzumab as pre-treatment.

Section 10 References

Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. Blood. 2014;124:2196−2202.

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Flynn JM, Byrd JC, Kipps TJ, et al. Obinutuzumab (GA101) 1,000 mg versus 2,000 mg in patients with chronic lymphocytic leukemia (CLL): results of the phase II GAGE (GAO4768g) trial. 2014. ASCO [https://meetinglibrary.asco.org/recod/92456/abstract]

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Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell–mediated B-cell cytotoxicity. Blood. 2010;115:4393-4402.

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Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. Blood. 2012;119:5126−5132.

Appendix 2 Section 6 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

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

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

- *RO7172508 Investigator's Brochure*
- *Obinutuzumab/RO7172508 combination - RO7172508 Investigator's Brochure*
- *Tocilizumab Investigator's Brochure*
- ~~RO7172508 Investigator's Brochure~~
- ~~—~~

Appendix 4 Clinical Laboratory Tests

[…]

Table 1 Protocol-Required Safety Laboratory Assessments

[…]

Other Tests	• sCEA*

*will be performed centrally *and locally*

Appendix 6 ***New Response Evaluation Criteria in Solid Tumors [RECIST] – Version 1.1*** *(Modified Excerpt from Original Publication with Addition of Supplementary Explanations)* was replaced with the new company standard text.

Appendix 7 : Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST) was added.