Official Title: An Open Label, Multicenter, Dose Escalation and Expansion, Phase 1 Study to Evaluate Safety, Pharmacokinetics, and Preliminary Anti Tumor Activity of RO7121661, a PD-1/TIM-3 Bispecific Antibody, in Patients with Advanced and/or Metastatic Solid Tumors

NCT Number: NCT03708328

Document Date: Protocol Amendment Version 5: 07-September-2021

PROTOCOL

TITLE:	**AN OPEN LABEL, MULTICENTER, DOSE ESCALATION AND EXPANSION, PHASE 1 STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, AND PRELIMINARY ANTI TUMOR ACTIVITY OF RO7121661, A PD-1/TIM-3 BISPECIFIC ANTIBODY, IN PATIENTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	NP40435
VERSION:	5
EUDRACT NUMBER:	2018-000982-35
IND NUMBER:	142844
TEST PRODUCT:	RO7121661
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 27 June 2018
DATE AMENDED:	Version 2: 12 June 2019 Version 3: 02 October 2019 Version 4: 04 June 2020 Version 5: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
07-Sep-2021 12:46:59	Company Signatory	[redacted]

PROTOCOL ACCEPTANCE FORM

TITLE:	**AN OPEN LABEL, MULTICENTER, DOSE ESCALATION AND EXPANSION, PHASE 1 STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, AND PRELIMINARY ANTI TUMOR ACTIVITY OF RO7121661, A PD-1/TIM-3 BISPECIFIC ANTIBODY, IN PATIENTS WITH ADVANCED AND/OR METASTATIC 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 5
RATIONALE

Protocol NP40435 has been amended to enable participants, who are benefitting from the therapy with RO7121661 at the end of the treatment period, to remain on treatment beyond the initial 24 months. Changes to the protocol, along with a rationale for each change, are summarized below.

- Section 2.3 and Section 6.5.1 were updated to add Covid-19 benefit/risk assessment and vaccine information.
- The Schedule of Assessment Table 1 (footnotes only), Section 4.1, Section 7.1, and Section 8.10.4 have been updated to add language to prolong the treatment period for participants who benefit from treatment.
- Medical Monitor language was updated in Section 5.1, Section 5.2, Section 5.4, Section 6.1.2, Section 6.5.1, Section 6.6, Section 7.1.1, Section 7.1.2, Section 8.3.8.1, Section 8.4, and Appendix 6 to reflect new guidelines on medical monitoring in accordance with ICH E6(R2) 4.3.1.
- In Appendix 6, the dose modification and treatment interruption sections have been removed to avoid redundancy with Sections 6.6 and 7.1.1. Information on immune-mediated myocarditis, Grade 1-2 has been removed from the management guidelines Table 6 to align with updates in the atezolizumab Investigator's Brochure. A section on hemophagocytic lymphohistiocytosis and macrophage activation syndrome was added to align language with other protocols studying in-house checkpoint inhibitors (including RO7121661).

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BSA	Body surface area
BsAb	Bispecific antibody
CIT	Cancer immunotherapy
CLss	Clearance
C_{max}	Maximum concentration
CNS	Central nervous system
COA	Clinical outcome assessments
CPI	Checkpoint inhibitor
CRCL	Creatinine clearance
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DCR	Disease control rate
DLCO	Diffusion capacity
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EOI	**End of infusion**
EOO	**End of observation**

Abbreviation	Definition
ESCC	**Esophageal squamous cell carcinoma**
ESF	Eligibility screening form
EU	European Union
EWOC	Escalation with overdose control
FDA	Food and Drug Administration
FFPE	Formaldehyde fixed-paraffin-embedded
FNA	Fine-needle aspiration
FSH	Follicle-stimulating hormone
HBcAb	Total hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoproteins
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormonal replacement therapy
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
imAE	Immune-mediated adverse event
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
iRECIST	Immune-related response evaluation criteria in solid tumors
IRR	Infusion-related reaction
IUD	Intrauterine device
IV	Intravenous

Abbreviation	Definition
IRT	Interactive response technology system
JMC	Joint Monitoring Committee
LAG-3	Lymphocyte-activation gene 3
LDL	Low-density lipoproteins
LPLV	Last participant, last visit
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MABEL	Minimum anticipated biological effect level
MAD	Multiple-ascending doses
mCRM	Modified continual reassessment method
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NGS	Next generation sequencing
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD	Pharmacodynamic
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PGIC	Patient global impression of change
PK	Pharmacokinetic
PT	Prothrombin time
QW	Every week
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QT	QT interval
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red blood cell
RBR	Research biosample repository

Abbreviation	Definition
RDE	Recommended dose for expansion
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RO	Receptor occupancy
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SDR	Stable disease rate
SEB	Staphylococcal enterotoxin B superantigen-induced
SoA	Schedule of activities
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
$T_{1/2}$	Half-life
TB	Tuberculosis
TCR	T-cell receptor
TIL	Tumor infiltrating lymphocytes
TIM-3	T-cell immunoglobulin and mucin domain 3
TKI	Tyrosine kinase inhibitor
TLR	Toll like receptor
T_{max}	Time of maximum concentration
TMB	Tumor mutational burden
TMDD	Target-mediated drug disposition
TPS	Tumor proportion score
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WES	Whole exome sequencing
WGS	Whole genome sequencing
WOCBP	Woman of childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**AN OPEN LABEL, MULTICENTER, DOSE ESCALATION AND EXPANSION, PHASE 1 STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, AND PRELIMINARY ANTI TUMOR ACTIVITY OF RO7121661, A PD-1/ TIM-3 BISPECIFIC ANTIBODY, IN PATIENTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
SHORT TITLE	**DOSE ESCALATION AND EXPANSION STUDY OF PD-1/TIM-3 BISPECIFIC ANTIBODY IN PATIENTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	NP40435
VERSION:	5
TEST PRODUCT:	RO7121661
PHASE:	I

RATIONALE

RO7121661, an anti-programmed death-1 (PD-1) / T-cell immunoglobulin and mucin domain 3 (TIM-3) bispecific antibody (BsAb), was designed to target dysfunctional tumor antigen-specific T lymphocytes (expressing PD-1 and TIM-3) in order to establish or re-establish an effective anti-tumor immune-response in cancer patients with high unmet medical need. This may result in improvement in the therapeutic response over currently available therapies and/or overcoming of primary resistance or emerging resistance against PD-1/programmed death-ligand 1 (PD-L1) checkpoint blockade in patients previously treated with PD-1 or PD-L1 checkpoint inhibitors (CPI experienced).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• **Dose Escalation:** Safety, tolerability, maximum-tolerated dose (MTD) and/or recommended dose for expansion (RDE)	• Nature and frequency of dose-limiting toxicities (DLTs) and other adverse events (AEs), pharmacodynamic (PD) and pharmacokinetic (PK) profile. • Incidence, nature and severity of AEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
• **Expansion**: Assessment of the anti-tumor activity of RO7121661.	• According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria: o Objective response rate (ORR). o Disease control rate (DCR); defined as (ORR)+stable disease rate (SDR). o Duration of response (DoR). o Progression free survival (PFS) defined as the time from the first study treatment (Day 1) to the first occurrence of progression per Investigator assessment or death from any cause, whichever occurs first.
Secondary	
• To characterize the immunogenicity profile of RO7121661 (Part A and B).	• Incidence of anti-drug antibodies (ADAs).
• To explore potential PD-1, TIM-3 and PD-1/TIM-3 specific PD biomarkers (Part B).	• Examine the profile and status of T cell proliferation/activation in tumor biopsies and peripheral blood.
• To investigate the single and multiple dose PK of RO7121661 (Part A and B).	• PK profiles and parameters derived for RO7121661.
• To explore degree of target binding of RO7121661 (in association with PK/PD) via receptor occupancy (RO).	• Evaluate RO via ex-vivo assay.
• To evaluate the safety and tolerability of RO7121661 (Part B). • To explore preliminary anti-tumor activity of RO7121661 (Part A).	• Incidence, nature and severity of AEs graded according to the NCI CTCAE v5.0. • According to RECIST Version 1.1 criteria: – Objective response rate (ORR). – Disease control rate (DCR). – Progression-free survival (PFS). – Duration of response (DoR).

OVERALL DESIGN

Study NP40435 is a first-in-human, open-label, multicenter, Phase I multiple-ascending dose (MAD) study of single agent RO7121661.

Study Design

The study consists of 2 parts (A and B):

Part A (RO7121661 Dose Escalation): To determine the MTD and/or RDE based on safety, tolerability, PK, and/or the PD profile of escalating doses of RO7121661 every 2 weeks (Q2W). If for specific cleared cohort(s) the safety, PK and/or RO and/or the biomarker profile need to be further characterized, additional participants, potentially enriched in certain indications and/or characteristics, may be enrolled.

Part B (RO7121661 Tumor-Specific Expansion Cohorts): To evaluate anti-tumor activity of the RDE of RO7121661 from Part A (2.1 g Q2W) and to confirm safety and tolerability in participants with selected tumor types. B1, B2, B4 and B5 expansions may be staggered, sequential or concurrent. Part B3 will not proceed prior to generation of data from the initial CPI experienced indication(s):

- **Part B1:** CPI experienced second line and beyond metastatic melanoma
- **Part B2:** CPI and platinum experienced second or third line PD-L1 positive NSCLC
- **Part B3:** PD-L1 positive, CPI naïve, first line NSCLC
- **Part B4:** CPI-naïve SCLC with prior failure of, progression on, or intolerance to standard therapy
- **Part B5:** CPI-naïve ESCC

Treatment Groups and Duration

The investigational medicinal product (IMP) is RO7121661.

Part A

RO7121661 will be administered IV with a flat dose. The starting dose will be 70 mg and the maximum dose explored will be 2.1 g. Since RO7121661 will be administered Q2W in Part A, the cycle length will be defined as 14 days.

This part of the study will enroll participants with solid tumors who have progressed on a cancer therapy or who are not amenable to standard of care. At least [redacted] DLT evaluable participants will be enrolled in each cohort during the dose escalation. Dose escalation will be carried out according to a modified continual reassessment method (mCRM) with escalation with overdose control (EWOC) design, with the aim of identifying the MTD/RDE of RO7121661.

The maximum total number of participants in the dose escalation portions of Part A will be approximately [redacted] DLT evaluable participants. A dose cohort can be extended to enroll additional participants, potentially enriched in certain tumor types and/or characteristics (approximately [redacted]) to confirm safety, PK and/or RO data.

Part B

Part B1 and/or B2 and/or B4 and/or B5 may commence upon completion of Part A. The starting dose of RO7121661 for Part B is 2.1 g as derived from the RDE in Part A determined by safety, PK and/or RO and/or the biomarker profile. Part B3 will not proceed prior to generation of data from the initial CPI experienced indication(s).

Patients enrolled in Part B expansions have more specific limitations of prior therapies for inclusion than during the dose escalation. Patients enrolled in Part B1 (CPI experienced melanoma) must have had treatment with approved anti-PD-L1/anti-PD-1 checkpoint inhibitors. Patients enrolled in Part B2 (CPI and platinum experienced, PD-L1 expression $\geq$ 1% NSCLC) must have had a checkpoint inhibitor and platinum chemotherapy. Patients enrolled in Part B3 (untreated, CIT naïve NSCLC with PD-L1 expression $\geq$ 50%) should not have had any prior therapy. Patients enrolled in Part B4 (CPI naïve SCLC) and B5 (CPI-naïve ESCC) should not have had any prior checkpoint inhibitor therapy but may have had chemotherapy. Specific details for Part B Expansions are included in the Inclusion and Exclusion Criteria.

In Part B (tumor specific expansion cohorts) approximately [redacted] participants will be included per indication. Part B cohorts may run in parallel staggered or sequentially.

Parts A and B

Participants will be treated with RO7121661 until disease progression, unacceptable toxicities, or withdrawal of consent. Participants may continue treatment with RO7121661 for 24 months *or longer if the participant is still benefitting from treatment at the time of the last visit at the end of the two-year period*. As with other immunotherapies, treatment beyond progressive disease according to RECIST Version 1.1 can be considered after consultation and agreement between the Sponsor and Investigator.

Length of Study

The duration of the study for each participant will be up to 27 months (Parts A and B), divided as follows:

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 (± 7) days after last treatment with RO7121661 for Part A; 90 (± .7) days after last treatment with RO7121661 for Part B.

Survival follow-up: 90 (± 7) days after last treatment with RO7121661; then every 3 months (± 2 weeks) for total 24-month study period after initial dose.

The treatment period may be prolonged past month 24 if the participant is still benefitting from treatment at the time of the last visit at the end of the two-year period. Participants may extend treatment within the ongoing study whether they are on treatment or are on a treatment pause at the 24-month time point. During the extended treatment period, the participant follows the schedule of assessments as indicated for "Subsequent Cycles." Participants will be treated until disease progression, unacceptable toxicities, or withdrawal of consent. For participants who extend their treatment, the safety follow-up will be performed 60 (± 7) days for Part A or 90 (± 7) days for Part B after the last treatment with RO7121661 and survival follow-up every 3 months (± 2 weeks) thereafter for a total of 48 months after initial dose, or end of the study.

End of Study

The end of the study is defined as the last participant's last visit (LPLV) per protocol (includes the safety follow-up visit 60 days (Part A) or 90 days (Part B) after last dose of study drug) or the date at which the last data point from the last participant required for statistical analysis is received (last participant, last observation), whichever is the latest date. Because of the exploratory nature of this clinical study, any part of its conduct can be discontinued at any time at the discretion of the Sponsor.

Data Monitoring Committee: In Part A, ongoing medical data review will be performed and regular teleconferences with participation of investigators and key representatives of the Sponsor will be scheduled. In Part B, a Joint Monitoring Committee (JMC) will monitor participants' safety. The JMC will consist of designated Sponsor personnel and independent clinical expert(s) (i.e., expert[s] independent from the Sponsor).

PARTICIPANT POPULATION

The study population consists of male and female participants with advanced and/or metastatic solid tumors.

Inclusion Criteria

General Inclusion Criteria for Parts A and B

Participants are eligible to be included in the study only if all of the following criteria apply prior to dosing on Cycle 1, Day 1.

Informed Consent

1. Signed written informed consent and ability to comply with the study protocol according to International Council for Harmonization 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 A only: Patients with advanced and/or metastatic solid tumors who have progressed on a cancer therapy, for whom no effective standard therapy exists, or who decline treatment with approved therapies.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 and a life expectancy of ≥ 12 weeks.
5. Adequate cardiovascular function:
    - New York Heart Association (NYHA) Heart Failure Stage ≤ 2.
    - Baseline-corrected QT (QTcF) interval ≤ 470 ms.
    - Resting systolic blood pressure ≤ 150 mmHg and diastolic blood pressure 100 mmHg (average of ≥ 3 readings on ≥ 2 sessions with short break between sessions) (no clinically significant hypertension).
    - Resting heart rate (HR) between 45-100 bpm (no clinically significant tachycardia).
6. Adverse events from any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade ≤ 1, except alopecia (any grade), vitiligo, endocrinopathy managed with replacement therapy and Grade 2 peripheral neuropathy.
7. Adequate hematological function: neutrophil count of ≥ 1.5×10^9 cells/L (1500/μl), platelet count of ≥ 100×10^9/L (100,000/μL), hemoglobin ≥ 9 g/dL (90 g/L), lymphocyte count of ≥ 0.5×10^9 cells/L (500/μL).
    - Hemoglobin must be stable for at least a week without need for packed red blood cell transfusion.
8. Adequate liver function: total bilirubin ≤ 1.5 × ULN; aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase ≤ 2.5 × ULN; with the following exceptions:
    - Participants with known Gilbert disease or hepatocellular carcinoma: serum bilirubin level ≤ 3 × ULN.
    - Participants with documented liver metastases: AST and ALT ≤ 5 × ULN.
    - Participants with documented liver or bone metastases: ALP ≤ 5 × ULN.
9. Adequate renal function: serum creatinine ≤ 1.5 × ULN or creatinine clearance by Cockcroft-Gault formula ≥ 50 mL/min for participants in whom, in the Investigator's judgment, serum creatinine levels do not adequately reflect renal function. Cockcroft-Gault glomerular filtration rate estimation:

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

10. Additional adequate laboratory parameters obtained:
    - Serum albumin ≥ 25 g/L (2.5 g/dL).
    - For participants not receiving therapeutic anticoagulation: Prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN or < 2 × ULN for participants with HCC.
    - For participants receiving therapeutic anticoagulation: stable anticoagulant regimen.
11. Negative HIV test at screening.
12. Negative hepatitis B surface antigen (HBsAg) test at screening.
13. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening.

- The HBV DNA test will be performed only for participants who have a positive total HBcAb test.

14. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening.

    The HCV RNA test will be performed only for participants who have a positive HCV antibody test.

15. Diagnosis of locally advanced and/or metastatic solid tumors with radiologically measurable disease according to RECIST v1.1.
    - Previously irradiated lesions should not be counted as target lesions unless clearly progressed after the radiotherapy.
    - Participants must have at least one measurable lesion (target lesion [TL]) not intended to be biopsied. Lesions that are intended to be biopsied should not be counted as target lesions.

Contraception

16. Male and/or female participants

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

    a). Female Participants

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

    - Not a woman of childbearing potential (WOCBP).
    - WOCBP, who:
        - Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 4 months after the final dose of RO7121661.
        - Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
        - Have a negative pregnancy test (blood) within the 7 days prior to the first study RO7121661 administration.

    b). Male Participants

    - During the treatment period and for at least 4 months after the final dose of RO7121661, agreement to:
        - Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year, with partners who are women of childbearing potential.
            - With pregnant female partners, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
        - Refrain from donating sperm during this period.

Specific Inclusion Criteria for Biopsies

17. Participants who are enrolled on the parts of the study where fresh biopsies are requested (i.e. biomarker cohort(s) and expansion cohorts B1, B2, B3, B4 and B5) must have at least one non-target tumor lesion accessible to biopsy per clinical judgment of the treating physician and consent to undergo mandatory fresh baseline and on-treatment biopsy. Participants in Part B, presenting with only one target lesion and no non-target lesions that can be biopsied may omit mandatory biopsies. *In such cases, the Medical Monitor is available to the Investigator to advise and answer any questions in this regard.* A lesion with evidence of progression by imaging (or measurement for cutaneous lesions) is preferred if it can be assessed accurately. Bone lesion biopsies, bronchoscopy/trans-bronchial biopsies, and cytology fine needle aspirates are not acceptable.

Specific Inclusion Criteria for Part B Expansion in CPI Experienced Patients

CPI experienced patients are defined in this study as those who have had prior treatment with an anti-PD-1 or anti-PD-L1 agent. Participants must meet the following additional criteria to be eligible for inclusion in Part B of the study if they are CPI experienced.

18. Participants with advanced and/or metastatic malignancies who have progressed on an anti-PD-L1/anti-PD-1 agent.
19. Participants who are considered to be deriving benefit from treatment beyond progression, as per clinical judgment, are not considered eligible. Screening tumor assessment should confirm progression.
20. Prior anti-PD-L1/PD-1 as monotherapy and/or as combination therapy may have been administered as indicated for the respective indications, with the exception of adjuvant therapy.

Melanoma Cohort (CPI-Experienced; Part B1)

21. Participants with histologically confirmed advanced or metastatic melanoma previously treated with approved anti-PD-L1/anti-PD-1 agents with or without approved anti-CTLA-4 therapy and up to one additional treatment regimen.
    - Eligibility of participants receiving previous treatment with non-approved anti PD-1 or anti-PD-L1 inhibitors or combination treatment with other non-approved agent(s) *may be discussed with* the Medical Monitor prior to enrollment. *The decision to enroll the patient in the study is the responsibility of the Investigator.*
22. Participants whose tumors have a known BRAFV600 mutation must also have experienced disease progression (during or after treatment) or intolerance with BRAF inhibitor(s) and/or MEK inhibitor(s) if treatment is available. Participants with BRAFV600 mutation but refusing such inhibitor(s), or not available to them, will be eligible.
23. Enrollment will be managed so that:
    - No more than approximately 10% of participants in this cohort will be participants with ocular (uveal) melanoma.
    - Up to 10 patients with primary resistance to CPI will initially be enrolled. This may be expanded if efficacy and or biomarker assessments for proof of mechanism warrant further exploration.
        - Primary resistance is defined as Investigator assessed best overall response of progressive disease within the first 10 weeks of anti-PD-L1/anti-PD-1 treatment.
            - If a scan within the first 10 weeks exists and shows progressive disease the patient is considered primary resistant (i.e. the scan result cannot be overruled by investigator assessment of clinical benefit).
            - Should a subsequent scan for the same line of treatment show clinical benefit after initial radiographic progression (i.e. pseudoprogression) the patient is not considered primary resistant.

NSCLC Cohort (CPI-Experienced; Part B2)

24. Participants with histologically confirmed advanced NSCLC previously treated with approved PD-L1/PD-1 inhibitors and platinum based chemotherapy, either sequentially or concurrently.
    - Eligibility of participants receiving previous treatment with non-approved anti PD-1 or anti-PD-L1 inhibitors or combination treatment with other non-approved agent(s) *may* be *discussed with* the Medical Monitor prior to enrollment. *The decision to enroll the patient in the study is the responsibility of the Investigator.*
25. Patients must be PD-L1 (+) defined as ≥ 1% PD-L1 expression based on immunohistochemistry using antibody clone 22c3, sp263 or 28-8. Expression will be determined in a fresh tumor biopsy collected during study screening or a possibly available archival sample, provided that the latter is not older than 12 months and has been obtained after failure of last CPI treatment line and prior to receiving study treatment.
26. Participants must have experienced Investigator assessed initial clinical benefit (stable disease or better) from most recent CPI therapy for at least 4 months.
    - If a scan within the first 4 months exists and shows progressive disease the patient is not eligible (i.e. the scan result cannot be overruled by Investigator assessment of clinical benefit).
    - Should a subsequent scan for the same line of treatment show clinical benefit after initial radiographic progression (i.e. pseudoprogression) the patient is eligible.
27. Patients should have had only one CPI and one platinum based regimen, whether sequentially or concurrently. The acceptable sequences are:
    - Platinum-based chemotherapy (1L) + CPI treatment (1L); i.e., study treatment is second line therapy
    - Platinum-based chemotherapy (1L) → CPI treatment (2L); i.e., study treatment is third line therapy
    - CPI treatment (1L) → Platinum-based chemotherapy (2L); i.e., study treatment is third line therapy
        – Adjuvant chemo-radiation treatment with anti-PD-1/PD-L1 inhibitors or consolidation treatment with anti-PD-1/PD-L1 after definitive chemo-radiation therapy is allowed but participants do require an additional line of anti-PD-1/PD-L1 treatment in the metastatic setting.

Specific Inclusion Criteria for Part B3 Expansion in PD L1 High, CPI Naïve, First Line NSCLC Cohort

28. Participants with histologically confirmed advanced NSCLC with PD-L1 high defined as ≥ 50% PD-L1 expression based on immunohistochemistry using antibody clone 22c3, sp263 or 28-8. Expression will be determined in a fresh tumor biopsy collected during study screening or a possibly available archival sample, provided that the latter is not older than 12 months and has been obtained after failure of last CPI treatment line and prior to receiving study treatment.

Specific Inclusion Criteria for Part B4 Expansion in CPI-Naïve SCLC Cohort

29. Participants must have histologically confirmed SCLC.
30. Participants may have had prior chemotherapy, radiation therapy or declined approved therapies for SCLC.

Additional Inclusion Criteria for Part B5: CPI Naïve Esophageal Squamous Cell Carcinoma

31. Participants whose major lesion was histologically confirmed squamous cell carcinoma or adenosquamous cell carcinoma of the esophagus.
32. Patients who have previously received not more than 1 prior lines of treatment for metastatic disease prior to enrolling to the study. The prior line must be a fluoropyrimidine and platinum-based regimen and patients must have experienced progressive disease.
33. Patients who underwent a radical resection (R0 resection confirmed) in conjunction with chemotherapy with fluoropyrimidine and platinum-based drugs including neo-adjuvant/adjuvant therapy and chemo-radiation (including patients who underwent chemo-radiation followed by salvage surgery) are allowed.
    - If recurrence was confirmed by imaging within 24 weeks after the last dose of the treatment, the therapy should be counted as equivalent to metastatic treatment. Such patients are eligible and do not require an additional line of therapy in the metastatic setting.
    - If recurrence occurred later than 24 weeks after the completion of the initial neo-adjuvant/adjuvant therapy the patients need to be exposed to an additional line of fluoropyrimidine and platinum-based drugs in the metastatic setting to be eligible for the study - unless the investigator considers the patient not eligible for the re-exposure with fluoropyrimidine and platinum-based drugs.

Exclusion Criteria

General Exclusion Criteria for Parts A and B

Participants are excluded from the study if any of the following criteria apply prior to dosing on Cycle 1, Day 1:

1. Pregnancy, lactation, or breastfeeding.
2. Known hypersensitivity to any of the components of RO7121661, including but not limited to hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

Medical Conditions

3. Known symptomatic central nervous system (CNS) metastases.
    - Participants with previously treated brain metastases may participate provided they:
    - Are stable (without evidence of progression by CT or MRI for at least 4 weeks prior to Cycle 1/Day 1).
    - Have no evidence of new or enlarging brain metastases within at least 4 weeks from Cycle 1/Day 1.
    - Are off systemic steroids for at least 28 days prior to Cycle 1/Day 1
4. Spinal cord compression not definitively treated with surgery and/or radiation or without evidence that disease has been clinically stable for $\geq$ 2 weeks before Cycle 1/Day 1.
5. Active or history of carcinomatous meningitis/leptomeningeal disease. Known asymptomatic CNS primary tumors or metastases if they have requirement for steroids or enzyme-inducing anticonvulsants in the last 28 days prior to Cycle 1/Day 1 screening.
6. Participants with an active second malignancy. Concurrent malignancy exceptions include: curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer and any previously treated early stage non-hematological malignancy that has been in remission for at least two years.
7. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders, and known autoimmune diseases or immune deficiency, or other

disease with ongoing fibrosis (such as scleroderma, pulmonary fibrosis, emphysema, neurofibromatosis, palmar/plantar fibromatosis, etc.).

8. Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
9. Severe dyspnea or requiring supplemental oxygen therapy at rest.
10. Significant cardiovascular/cerebrovascular vascular disease within 6 months prior to Day 1 of study drug administration, including any of the following:
    - hypertensive crisis/encephalopathy
    - unstable angina
    - transient ischemic attack/stroke
    - congestive heart failure (for NYHA classification, refer to inclusion criteria)
    - serious cardiac arrhythmia requiring treatment (exceptions are atrial fibrillation, paroxysmal supraventricular tachycardia)
    - history of thromboembolic events (such as myocardial infarction, stroke or pulmonary embolism)
11. Known active or uncontrolled bacterial, viral, fungal, mycobacterial (including but not limited to tuberculosis [TB] and typical mycobacterial disease), parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 4 weeks prior to the start of drug administration.
12. Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease.
13. Major surgical procedure or significant traumatic injury (excluding biopsies) within 28 days prior to Cycle 1, Day 1 (i.e., first RO7121661 infusion), or anticipation of the need for major surgery during the course of the study.
14. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the participant at high risk from treatment complications.
15. Dementia or altered mental status that would prohibit informed consent.
16. Uncontrolled pleural effusion (with the exception of participants with indwelling catheters, e.g. PleurX®), pericardial effusion, or ascites requiring recurrent drainage procedures (expected to occur once monthly or more frequently).
17. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
    - Participants with a history of autoimmune-mediated hypothyroidism or endocrinopathy who are on thyroid-replacement hormone or appropriate replacement therapy are eligible for the study.
    - Participants with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Participants with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        - Rash must cover $< 10\%$ of body surface area
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids

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

Prior/Concomitant Therapy

18. Vaccination with live vaccines within 28 days prior to the start of treatment.
19. For Part A Part B1 (CPI experienced melanoma patients) and B2 (CPI and platinum experienced NSCLC patients), prior treatment with CPIs, immunomodulatory monoclonal antibodies (mAbs), and/or mAb-derived therapies is allowed, with the following exceptions:
    - 4 weeks have elapsed between the last dose of prior anti-PD-1 and the proposed Cycle 1, Day 1
    - 5 half-lives or 28 days (whichever is shorter) have elapsed from prior treatment with specific immunomodulators, TLR agonists, inhibitors of IDO/TDO, or agonists (e.g., OX40)
    - Prior treatment with adoptive cell therapies, such as CAR-T therapies is not permitted
20. Prior treatment with a TIM-3 inhibitor is prohibited.
21. Concurrent therapy with any other investigational drug (defined as treatment for which there is currently no regulatory authority-approved indication) $<$ 28 days or 5 half-lives of the drug, whichever is shorter, prior to the first RO7121661 administration on Cycle 1, Day 1 is prohibited.
22. Immuno-modulating agents:
    - Last dose with any of the following agents, for example, etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, or efalizumab (or similar agents) $<$ 28 days prior to Cycle 1, Day 1 is prohibited.
    - Regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease) is prohibited.
23. Chronic use of steroids (excluding topical and inhaled) and concurrent high doses of systemic corticosteroids will not be allowed. Participants receiving baseline corticosteroid therapy ($>$ 10 mg prednisone/day or equivalent) within 1 week prior to the first dose of study drug are excluded.
24. Radiotherapy within the last 4 weeks before start of study drug treatment is not allowed, with the exception of limited palliative radiotherapy.
25. *Enrollment of participants who require blood transfusion (before and after the start of the study) is at the discretion of the Investigator. The Medical Monitor/Sponsor is available to the Investigator to advise and answer any question as needed.*

Specific Exclusion Criteria for Part B1 and Part B2 Expansion cohorts (CPI experienced patients)

26. Any history of an immune-mediated Grade 4 adverse event attributed to prior cancer immunotherapy (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase)
27. Any history of an immune-mediated adverse event attributed to prior CIT (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase) that resulted in permanent discontinuation of the prior immunotherapeutic agent.
28. All immune-mediated adverse events related to prior immunomodulatory therapy (other than endocrinopathy managed with replacement therapy or stable vitiligo) must have resolved completely to baseline. Participants treated with corticosteroids for immune-mediated adverse events except for corticosteroids replacement therapy for adrenal insufficiency (provided that the patient receives $\leq$ 10 mg prednisone/day or equivalent),

must demonstrate absence of related symptoms or signs for ≥ 4 weeks following discontinuation of corticosteroids.

Specific Exclusion Criteria for Part B3 Expansion (1st line CIT naïve patients)

29. Prior therapy for metastatic disease is not permitted i.e., treatment with any immune CPIs (such as anti PD L1/PD 1, CTLA 4), immunomodulatory mAbs, other immunomodulator therapies, chemotherapy or TKIs.
30. Adjuvant anti-PD-1 or anti-PD-L1 therapy is not allowed. Adjuvant chemotherapy is permitted as long as treatment was administered > 6 months prior to Cycle 1, Day 1.

Specific Exclusion Criteria for NSCLC patients (Part B2)

31. NSCLC patients with the following mutations, rearrangements, translocations are not eligible for Part B2: EGFR; ALK; ROS1, BRAFV600E, NTRK

Specific Exclusion Criteria for Part B4 Expansion (CPI-naïve SCLC patients)

32. Prior therapy with any immune CPIs (such as anti-PD-L1/PD-1, anti-CTLA-4), is not permitted.

Specific Exclusion Criteria for Part B5: CPI Naïve Esophageal Squamous Cell Carcinoma

33. Prior therapy with any immunomodulatory agents including CPIs (such as anti-PD-L1/PD-1, anti-CTLA-4), is not permitted.

NUMBER OF PARTICIPANTS

The maximum planned enrollment for this study is approximately 270-280 participants for both Parts A and B.

For the dose escalation stage in Part A, up to [redacted] DLT evaluable participants are planned for the Q2W schedule with an additional [redacted] participants if confirmation of safety, PK, RO and/or biomarkers are needed prior to opening Part B cohorts. The exact sample size cannot be pre-determined and depends on the number of cohorts needed to reach the MTD/RDE with the maximum planned dose set at 2.1 g.

Up to approximately [redacted] participants may be enrolled in the expansion stages across the indication-specific cohorts in Part B.

CONCOMITANT MEDICATIONS

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 *can advise if* there are any questions regarding concomitant or prior therapy.

All concomitant medications *or vaccines* should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). All therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

Radiotherapy

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

- Days where RO7121661 is administered.
- During the DLT evaluation window.
  - If radiotherapy is administered during the DLT evaluation window, the participant will not be evaluable.

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 and therapy for pre-existing conditions, unless the rationale for exception is discussed and clearly documented.

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

Investigational or unlicensed/unapproved agents

Immunotherapy/radio-immunotherapy

Chemotherapy / targeted therapy

Radiotherapy (with the exception of limited field palliative radiotherapy).

Biologic agents (e.g., bevacizumab, cetuximab).

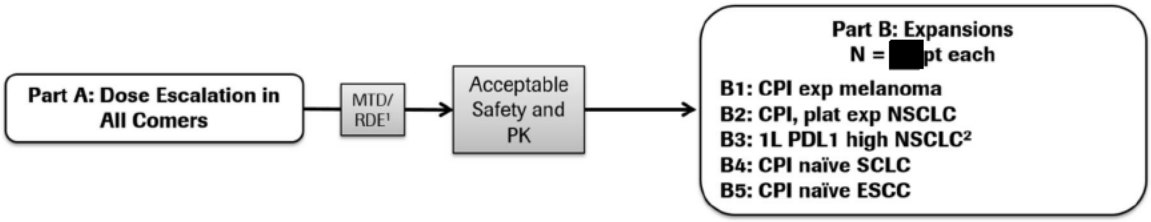
Chronic use of steroids (inhaled and topical steroids are permitted) at baseline of $>$ 10 mg of prednisone/day (or equivalent). Concurrent high doses of systemic corticosteroids will not be allowed.

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.

Figure 1 Overview of Study Design



[1] RDE= recommended dose for expansion.

[2] CIT naïve NSCLC will start after generation of data from CPI experienced patients.

1.3 SCHEDULE OF ACTIVITIES

The schedule of activities for the Q2W schedule is provided in Table 1. The hourly schedule for Part A and Part B is provided in Table 2 and Table 3, respectively.

Table 1 Schedule of Activities: Q2W regimen for Part A and B1, 2, 3, 4, and 5

Q2W regimen Cycle length 14 days	Screening	Cycle 1				*Cycles 2*			Subsequent cycles	Study Completion/Early Termination Visit[12]	Safety Follow up Visit	Survival Follow up Visit[13]	Unscheduled Safety
Day	Up to 28 Days	1	2	3	5 *(+/- 1)*	1	2	5 *(+/- 1)*	1	28 (+/-7) days after last dose	60 (+/-7) days (Part A), 90 (+/- 7) days (Part B) post last dose	90 (+/-7) days post last dose, then every 3 months (+/- 2wks)	e.g. In the event of an IRR or hypersensitivity event ≥G2 or AE leading to dose reduction or delay
Time Relative (h)		0	24	48	96	0	24	96	0	***	***	***	***
Assessments													
Informed Consent [1]	x												
Review Eligibility Criteria	x												
Demography	x												
Medical History	x												
Royal Marsden Risk Score	x												
Previous and Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x
Cancer History	x												
Physical Exam [2,4]	x	x				x			x	x	x		x
Vital Signs [2, 14]	x	x	x	x	x	x	x	x	x	x	x		x
ECOG Performance Status[2]	x	x				x			x	x	x		
Triplicate ECG 12-Lead [2, 3]	x	x				x			x	x	x		x
Adverse Events [5]	x	x	x	x	x	x	x	x	x	x	x	x	x
RO7121661 administration		x				x			x				
Tumor Assessment [6]	x								x[6]	x[6]			
Local Laboratory Assessments [2]													
Coagulation [9]	x	x				x			x[9]	x	x		x
Immunology [15]	x												
TSH, free T3 (or total T3), and free T4 [16]	x								x[16]		x		
Auto Antibody Panel [7]	x								x[7]		x		
Viral Serology [8]	x												
Hematology	x	x	x	x	x	x	x	x	x	x	x		x
Blood chemistry	x	x	x	x	x	x	x	x	x	x	x		x
Lipid Panel [10]	x	x							x[10]	x	x		
Urinalysis	x	x		x	x	x	x		x	x	x		
Pregnancy Test [11]	x					x			x[11]	x	x		
Central Laboratory Assessments													
PK RO7121661	Refer to Hourly Schedule of Assessments for specific Sample Collection Timepoint Details												
ADA to RO7121661													
Receptor Occupancy													
PD Plasma													
PD Serum													
IgE/Tryptase													
PD Whole Blood Flow Cytometry													
Whole Blood RNA													
bTMB													
ctDNA													
Archival Tumor Sample													
Fresh Tumor Biopsy													
RBR Sample (Saliva DNA)													

Table 1 Schedule of Activities: Q2W regimen for Part A and B1, 2, 3, 4, and 5 (cont.)

1. Informed consent must be obtained before any study-specific procedures. (Note: A separate consent form is required for RBR testing). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used and such tests do not need to be repeated for screening.
2. If indicated assessments are performed within 72 hours before dosing days, the assessments do not have to be repeated on the first day of that cycle. If performed on the day of study drug administration they must be done PRIOR to study drug administration. 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.
3. Triplicate 12-lead ECG recordings (i.e., 3 qualitatively acceptable ECGs without artifacts) must be obtained at screening, at pre-infusion, end of infusion (EOI) and within windows provided at each specified time-point. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection. Unscheduled 12-lead ECGs are ONLY REQUIRED as clinically indicated, e.g. there is evidence of QT prolongation on previous ECG assessments. In addition, single ECGs will be recorded in the case of an IRR. Recording must be done prior to PK sampling.
4. Complete physical exam (including weight and height at screening only) must be performed during screening, Day 1 of each treatment cycle before study treatment administration, at any unscheduled safety visit, and at study treatment discontinuation, and at the 60-day (Part A) / 90-day (Part B) safety follow‑up. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.
5. Adverse Events: After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until study completion or patient discontinuation, whichever is later. After this period, investigators should report only SAEs that are believed to be related to prior treatment with study drug. Serious adverse events occurring after signature of informed consent but prior to the first infusion of study treatment are reportable according to local regulations. Serious adverse events related to study procedures are reportable following signature of informed consent. For serious adverse events (SAEs) prior to first dose, a corresponding AE page should also be completed.
6. Tumor assessments will include contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis as well as the site of the primary tumor (if applicable). Measurable lesions will be assessed at Screening and then every 8 weeks (± 7 days) after Cycle 1, Day 1 for the first year; and every 12 weeks (± 7 days) thereafter until disease progression or treatment discontinuation (whichever occurs last), initiation of a new line of therapy or death. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used as the screening tumor assessment rather than repeating the scans. Evaluation of tumor response will be based on RECIST v1.1 criteria (see Appendix 7). Every time a tumor assessment is done, a PD Serum sample should be collected.

Table 1 Schedule of Activities: Q2W regimen for Part A and B1, 2, 3, 4, and 5 (cont.)

7. The auto-antibody panel will be assessed at Screening, pre-dose Cycles 3 and 9, and every 6 cycles thereafter. In participants who develop signs and/or symptoms suggestive of auto-immune disease while on-treatment, the auto-antibody panel (anti-nuclear antibody, anti−double-stranded deoxyribonucleic acid (DNA), circulating anti-neutrophil cytoplasmic antibody [cANCA], and perinuclear anti neutrophil cytoplasmic antibody [pANCA]) should be repeated. Patients with confirmed positive serology of at least one of the auto-antibody panel during the course of the study should be discussed between Sponsor and Investigators, and if judged clinically relevant, could be referred to a specialist to exclude an underlying auto-immune disease.
8. 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 RO7121661.
9. Coagulation sampling (including prothrombin time [PT], international normalized ratio [INR], and activated partial prothrombin time [aPTT]) will be performed at the specified time-points (prior to dosing). After Cycle 6, coagulation sampling will be performed at every visit when tumor assessment is performed. Additional coagulation parameters (i.e., anti-thrombin III, fibrinogen, PT, fibrin degradation products, D-dimer) maybe be assessed according to clinical judgment.
10. Lipid panel is to be obtained at Screening, Cycle 1, Day 1 and then every 8 weeks (±7 days) after Cycle 1/Day 1 and at indicated time-points.
11. Serum pregnancy test at screening, within 7 days prior to first dose, every cycle (urine or serum), discontinuation visit, and at the safety follow-up visit; a urine or serum pregnancy test will be performed. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Results must be obtained and reviewed prior to administration of RO7121661. Unscheduled pregnancy test (urine or serum) can be done anytime during the study if clinically indicated.
12. P*articipants* who discontinue will be asked to return to the clinic for an early termination visit within 28 (± 7) days after the last dose. In some instances, the visit at which a response assessment shows progressive disease may be used as the early termination visit. Alternatively, the study completion visit may be completed at the end of study *if a participant remains on a treatment pause to that day.*
13. Survival follow-up visit to be performed 90 (± 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 up to 24 months *(48 months for the extended treatment period)* from 1st dose for overall survival. For participants in Part B, the safety follow-up visit will occur on the same day as the first survival follow-up visit. Post-study anti-cancer therapies should be collected and reported as appropriate in the electronic case report form (eCRF).

Table 1 Schedule of Activities: Q2W regimen for Part A and B1, 2, 3, 4, and 5 (cont.)

14. Vital signs include measurements of heart rate, respiratory rate, systolic and diastolic blood pressures (while the patient is in a supine position), and temperature. For each visit, only those vital signs that are obtained prior to study drug administration or that constitute an adverse event (e.g., temperature for event of fever) or a primary manifestation of an adverse event (e.g., blood pressure associated with an infusion-related reaction or heart rate associated with an arrhythmia) should be recorded in the eCRF.
15. At Screening, an immunology sample will be taken for quantitative immunoglobulins (Ig): IgA, IgG, IgM, and IgE.
16. TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 3 and every three cycles thereafter (i.e., Cycle 6/ Day 1; Cycle 9/ Day 1; Cycle 12, Day 1; Cycle 15, Day 1; Cycle 18, Day 1; etc.). An endocrinologist should be consulted if an endocrinopathy is suspected.

Table 2 Schedule of Activities: Q2W regimen for Part A; hourly

Q2W regimen Cycle length 14 days	Day	Scheduled Time (h)[a]	Time Window	Vital Signs[b]	Triplicate ECG - 12 Lead[c]	Hematology	Blood Chemistry	PK Sample[d]	ADA RO7121661[e]	Receptor Occupancy	PD Serum[l]	PD Plasma	IgE/ Tryptase[g]	WGS[k]	Archival Tumor Sample[f]	Fresh Tumor Biopsy[h]	RBR Saliva DNA Optional[i]
Screening				x	x	x	x								x	x	
Cycle 1	Day 1	PreDose	-4h	x	x	x	x	x	x	x	x	x		x			x
		1/2 EOI	+/- 5 min					x			x						
		EOI	+ 10 min	x	x	x	x	x		x	x						
		0.5	+/- 10 min	x													
		2	+/- 15 min	x				x			x						
		4	+/- 1 h	x				x			x						
		8	+/- 1 h	x		x	x										
	Day 2	24	+/- 2 h	x		x	x	x			x	x					
	Day 3	48	+/- 2 h	x		x	x	x			x						
	Day 5	96	+/- 24 h	x		x	x	x			x						
	Day 8	168	+/- 24 h					x		x	x	x					
	Day 12	264	+/- 24 h					x			x						
Cycle 2	Day 1	PreDose	-4h	x	x	x	x	x	x	x	x	x					
		EOI	+ 10 min	x	x			x									
		4	+/- 1 h	x				x									
	Day 2	24	+/- 2 h	x		x	x	x									
	Day 5	96	+/- 24 h	x		x	x	x									
Cycle 3	Day 1	PreDose	-4h	x	x	x	x	x	x	x	x	x				x	
		EOI	+ 10 min	x	x			x									
		EOO	+/- 15 min	x													
Cycle 4	Day 1	PreDose	-4h	x	x	x	x	x	x		x						
		EOI	+ 10 min	x	x			x									
		EOO	+/- 15 min	x													
Cycle 5	Day 1	PreDose	-4h	x	x	x	x	x	x	x	x	x					
		1/2 EOI	+/- 5 min					x									
		EOI	+ 10 min	x	x			x		x							
		2	+/- 15 min					x									
	Day 2	24	+/- 2 h					x				x					
	Day 5	96	+/- 24 h					x									
	Day 8	168	+/- 24 h					x		x		x					

Table 2 Schedule of Activities: Q2W regimen for Part A; hourly (cont.)

Q2W regimen Cycle length 14 days	Day	Scheduled Time (h)[a]	Time Window	Vital Signs[b]	Triplicate ECG - 12 Lead[c]	Hematology	Blood Chemistry	PK Sample[d]	ADA RO7121661[e]	Receptor Occupancy	PD Serum	PD Plasma	IgE/ Tryptase[g]	WGS [k]	Archival Tumor Sample[f]	Fresh Tumor Biopsy [h]	RBR Saliva DNA Optional [i]
Subsequent Cycles	Day 1	PreDose	-4h	x	x	x	x	x	x	x [j]	x [l]	x [j]					
		EOI	+ 10 min	x	x			x									
		EOO	+/- 15 min	x													
In the event of an IRR or hypersensitivity event ≥G2 or AE leading to dose reduction or delay				x	x	x	x	x			x	x	x				
Study Completion/Early Termination Visit		At Visit		x	x	x	x	x	x	x	x	x					
Safety Follow up Visit (60d Part A; 90d Part B)		At Visit		x	x	x	x	x	x	x	x	x					
Unscheduled Visits		At Visit						x	x	x	x	x	x			x	

a) Assessments should be performed relative to RO7121661 infusion. When not specified, assessments should be performed relative to the end of the RO7121661 infusion.

b) Vital signs include measurements of heart rate, respiratory rate, systolic and diastolic blood pressures (while the participant is in a seated or supine position), and temperature. For the first infusion of RO7121661, measure vital signs within 60 minutes before the infusion, every 15 (± 5) minutes during the infusion and at the time-points specified or if clinically indicated. For subsequent infusions, measure vital signs within 60 minutes before the infusion, during the infusion if clinically indicated and at the time-points specified or if clinically indicated. For each visit, only those vital signs that are obtained prior to study drug administration or that constitute an adverse event (e.g., temperature for event of fever) or a primary manifestation of an adverse event (e.g., blood pressure associated with an infusion-related reaction or heart rate associated with an arrhythmia) should be recorded in the eCRF. Vital signs to be taken on Day 2 of Cycle 6 through Cycle 9 as noted on Main SOA Table.

c) Triplicate 12-lead ECG recordings (i.e., 3 qualitatively acceptable ECGs without artifacts) must be obtained at screening, at pre-infusion, EOI and at the time-points specified. Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 5 minutes apart. Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done prior to PK sampling.

d) Blood for PK of RO7121661 and for PD should be drawn at the indicated time-points relative to the end of the RO7121661 infusion. During the course of the study, PK/PD sampling time-points may be modified based on emerging data to ensure the PK/PD of RO7121661 can be adequately characterized. When more than one blood draw assessment at the same time point is required it should be taken in the order of safety, PK, ADA, then PD.

Table 2 Schedule of Activities: Q2W regimen for Part A; hourly (cont.)

e) Blood for ADA determination of RO7121661 should be taken at indicated time-points up to Cycle 5. Thereafter, blood for ADA determination of RO7121661 will be taken at Cycle 7, Day 1, and every 6 cycles afterwards (Cycle 13, Cycle 19, Cycle 25, etc.). Blood for ADA determination should always be taken pre-dose.

f) Participants with confirmed availability of representative archival tumor specimens in formalin-fixed, paraffin-embedded (FFPE) blocks (preferred) or unstained slides, with an associated pathology report.

g) IgE and tryptase samples will be collected for central and local analysis if a participant experiences a Grade ≥ 2 IRR for the first time with the second or subsequent study drug infusion or with clinical signs of hypersensitivity reaction at any time of the conduct of the study. A second sample for central IgE/tryptase analysis will be collected approximately 48 hours after onset of the reaction.

h) No biopsies are required in Part A dose escalation. If dose cohort is extended in Part A to confirm safety, PK and/or RO and/or the biomarker profile, then fresh tumor biopsies are mandatory for these additional participants, unless otherwise specified by the Sponsor. Screening sample should be collected after eligibility is confirmed. Post dose sample to be collected $+2/-1$ day[s] from scheduled timepoint.

i) Samples for RBR DNA saliva will be collected on Day 1 from all participants who signed RBR ICF prior to study drug (RO7121661) infusion. If the RBR DNA saliva sample is not collected during the scheduled visit, it may be collected at any time during the conduct of the clinical study.

j) Drug RO and PD-Plasma samples will be collected at Cycles 9, 22, 35 and 48.

k) If sample is missed on Cycle, 1 Day 1, it can be collected at any time during the conduct of the study.

l) After Cycle 5 the PD Serum sample should be collected every time a tumor assessment is done (every 8 weeks (± 7 days) thereafter for the first year; and every 12 weeks (± 7 days) thereafter until disease progression, treatment discontinuation or death).

Table 3 Schedule of Activities: Q2W regimen for Part B1, 2, 3, 4 and 5; hourly

Q2W regimen Cycle length 14 days	Day	Scheduled Time (h)[a]	Time Window	Vital Signs[b]	Triplicate ECG - 12 Lead[c]	Hematology	Blood Chemistry	PK Sample[d]	ADA RO7121661[e]	PD Serum[m]	PD Plasma	IgE/ Tryptase[g]	Whole Blood Flow Cytometry[h]	Whole Blood RNA	bTMB	ctDNA	WGS[l]	Archival Tumor Sample[f]	Fresh Tumor Biopsy[j]	RBR Saliva DNA Optional[i]
Screening				x	x	x	x								x[k]	x[k]		x	x	
Cycle 1	Day 1	PreDose	-4h	x	x	x	x	x	x	x	x		x	x			x			x
		1/2 EOI	+/- 5 min					x		x										
		EOI	+ *10* min	x	x	x	x	x		x										
		0.5	+/- 10 min	x																
		2	+/- 15 min	x				x		x										
		4	+/- 1 h	x				x		x										
		8	+/- 1 h	x		x	x													
	Day 2	24	+/- 2 h	x		x	x	x		x	x		x							
	Day 3	48	+/- 2 h	x		x	x	x		x										
	Day 5	96	*+/- 24 h*	x		x	x	x		x										
	Day 8	168	+/- 24 h					x		x	x		x							
	Day 12	264	+/- 24 h					x		x										
Cycle 2	Day 1	PreDose	-4h	x	x	x	x	x	x	x	x		x							
		EOI	+ *10* min	x	x			x												
		4	+/- 1 h	x				x												
	Day 2	24	+/- 2 h	x		x	x	x												
	Day 5	96	*+/- 24 h*	x		x	x	x												
Cycle 3	Day 1	PreDose	-4h	x	x	x	x	x	x	x	x		x	x[k]	x[k]	x[k]			x	
		EOI	+ *10* min	x	x			x												
		EOO	+/- 15 *min*	x																
Cycle 4	Day 1	PreDose	-4h	x	x	x	x	x	x	x										
		EOI	+ *10* min	x	x			x												
		EOO	+/- 15 *min*	x																
Cycle 5	Day 1	PreDose	-4h	x	x	x	x	x	x	x	x		x		x	x				
		1/2 EOI	+/- 5 min					x												
		EOI	+ *10* min	x	x			x												
		2	+/- 15 min					x												
	Day 2	24	+/- 2 h					x			x		x							
	Day 5	96	*+/- 24 h*					x												
	Day 8	168	+/- 24 h					x			x		x							

Table 3 Schedule of Activities: Q2W regimen for Part B1, 2, 3, 4 and 5; hourly (cont.)

Q2W regimen Cycle length 14 days	Day	Scheduled Time (h)[a]	Time Window	Vital Signs[b]	Triplicate ECG - 12 Lead[c]	Hematology	Blood Chemistry	PK Sample[d]	ADA RO7121661[e]	PD Serum	PD Plasma	IgE/ Tryptase[g]	Whole Blood Flow Cytometry[h]	Whole Blood RNA	bTMB[k]	ctDNA[k]	WGS[l]	Archival Tumor Sample[f]	Fresh Tumor Biopsy[j]	RBR Saliva DNA Optional[i]
Subsequent Cycles	Day 1	PreDose	-4h	x	x	x	x	x	x	x[m]	x[h]		x[h]							
		EOI	+ 10 min	x	x			x												
		EOO	+/- 15 min	x																
In the event of an IRR or hypersensitivity event ≥G2 or AE leading to dose reduction or delay				x	x	x	x	x		x	x	x								
Study Completion/Early Termination Visit		At Visit		x	x	x	x	x	x	x	x		x							
Safety Follow up Visit (60d Part A; 90d Part B)		At Visit		x	x	x	x	x	x	x	x		x							
Unscheduled Visits		At Visit						x	x	x	x	x	x		x	x			x	

a) Assessments should be performed relative to RO7121661 infusion. When not specified, assessments should be performed relative to the end of the RO7121661 infusion.

b) Vital signs include measurements of heart rate, respiratory rate, systolic and diastolic blood pressures (while the participant is in a seated or supine position), and temperature. For the first infusion of RO7121661, measure vital signs within 60 minutes before the infusion, every 15 ($\pm$ 5) minutes during the infusion and at the time-points specified or if clinically indicated. For subsequent infusions, measure vital signs within 60 minutes before the infusion, during the infusion if clinically indicated and at the time-points specified or if clinically indicated. For each visit, only those vital signs that are obtained prior to study drug administration or that constitute an adverse event (e.g., temperature for event of fever) or a primary manifestation of an adverse event (e.g., blood pressure associated with an infusion-related reaction or heart rate associated with an arrhythmia) should be recorded in the eCRF. Vital signs to be taken on Day 2 of Cycle 6 through Cycle 9 as noted on Main SOA Table.

c) Triplicate 12-lead ECG recordings (i.e., 3 qualitatively acceptable ECGs without artifacts) must be obtained at screening (within 7 days before first dose of RO7121661), at pre-infusion, EOI and at the time-points specified. Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 5 minutes apart. Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done prior to PK sampling.

d) Blood for PK of RO7121661 and for PD should be drawn at the indicated time-points relative to the end of the RO7121661 infusion. During the course of the study, PK/PD sampling time-points may be modified based on emerging data to ensure the PK/PD of RO7121661 can be adequately characterized. When more than one blood draw assessment at the same time point is required it should be taken in the order of safety, PK, ADA, then PD.

Table 3 Schedule of Activities: Q2W regimen for Part B1, 2, 3, 4 and 5; hourly (cont.)

e) Blood for ADA determination of RO7121661 should be taken at indicated time-points up to Cycle 5. Thereafter, blood for ADA determination of RO7121661 will be taken at Cycle 7, Day 1, and every 6 cycles afterwards (Cycle 13, Cycle 19, Cycle 25, etc.). Blood for ADA determination should always be taken pre-dose.

f) Participants with confirmed availability of representative archival tumor specimens in formalin-fixed, paraffin-embedded (FFPE) blocks (preferred) or unstained slides, with an associated pathology report.

g) IgE and tryptase samples will be collected for central and local analysis if a participant experiences a Grade ≥ 2 IRR for the first time with the second or subsequent study drug infusion or with clinical signs of hypersensitivity reaction at any time of the conduct of the study. A second sample for central IgE/tryptase analysis will be collected approximately 48 hours after onset of the reaction.

h) PD-Plasma and blood flow cytometry samples will be collected at Cycles 9, 22, 35 and 48.

i) Samples for RBR DNA saliva will be collected on Day 1 from all participants who signed RBR ICF prior to study drug (RO7121661) infusion. If the RBR DNA saliva sample is not collected during the scheduled visit, it may be collected at any time during the conduct of the clinical study.

j) Screening sample should be collected after eligibility is confirmed unless the fresh biopsy sample is needed to confirm patient eligibility. Post dose sample to be collected $+2/-1$ day[s] from scheduled timepoint. If the patient progresses and discontinues treatment before the scheduled biopsy timepoint, the biopsy should be collected at time of treatment discontinuation. Additional biopsy at time of PR, SD, PD or any other timepoint of interest based on participants' course of disease may be taken after discussion between the Investigator and the Sponsor.

k) bTMB and ctDNA should be collected on the same day as the tumor biopsy sample.

l) If sample is missed on Cycle 1, Day 1, it can be collected at any time during the conduct of the study.

m) After cycle 5 the PD Serum sample should be collected every time a tumor assessment is done every 8 weeks (± 7 days) thereafter for the first year; and every 12 weeks (± 7 days) thereafter until disease progression, treatment discontinuation or death).

2. INTRODUCTION

2.1 STUDY RATIONALE

RO7121661, an anti-programmed death-1 (PD-1) / T-cell immunoglobulin and mucin domain 3 (TIM-3) bispecific antibody (BsAb), was designed to target dysfunctional tumor antigen-specific T lymphocytes (expressing PD-1 and TIM-3) in order to establish or re-establish an effective anti-tumor immune-response in cancer patients with high unmet medical need. This may result in improvement in the therapeutic response over currently available therapies and/or overcoming of primary resistance or emerging resistance against PD-1/programmed death-ligand 1 (PD-L1) checkpoint blockade in patients previously treated with PD-1 or PD-L1 checkpoint inhibitors (CPI experienced). Exploration of activity in patients without prior CPI exposure (i.e., CPI naïve) is also planned.

NP40435 is a first in human, open label, multicenter, Phase I study to determine the maximum tolerated dose (MTD) and/or a recommended dose for expansion (RDE) that will allow exploration of the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity of RO7121661.

The rationale for the study design is provided in Section 4.3.

2.2 BACKGROUND

Cancer remains a major cause of death worldwide despite several new agents providing survival benefits to patients. Many cancer indications have a poor prognosis, and the management of most advanced solid tumors remains challenging because of the high rate of tumor recurrence or the development of distant metastases.

2.2.1 Non-Small Cell Lung Cancer Patients: Checkpoint Inhibitor Experienced and Naïve

Treatment of patients with advanced non-small cell lung cancer (NSCLC) has undergone significant changes with the development of immune CPI monoclonal antibodies (mAbs) to anti-PD-1/PD-L1 e.g., pembrolizumab, nivolumab or atezolizumab or durvalumab (see recent reviews: Hashimoto et al 2018; Thommen and Schumacher 2018; Zappasodi et al 2018) now commonly used in patients without mutations or rearrangements in the EGFR, ALK and ROS genes. Initial approval was in patients who had prior platinum based chemotherapy. Pembrolizumab approval was supported by the KEYNOTE-001 Phase I trial in patients with ≥50% PD-L1 (Garon et al 2015) and extended by the KEYNOTE-010 Phase III trial in patients with≥1% PD-L1 (Herbst et al 2016). Nivolumab was approved in patients regardless of PD-L1 status, initially in advanced squamous NSCLC (Brahmer et al 2015) and subsequently in non-squamous NSCLC (Borghaei et al 2015). Atezolizumab was approved in patients independent of PD-L1 status and histology (squamous and non-squamous) based on the POPLAR Phase II (Fehrenbacher et al 2016) and the OAK Phase III trials (Rittmeyer et al 2017).

Pembrolizumab has also received approval for treatment-naïve patients with advanced NSCLC without driver mutations and with tumor proportion score (TPS) ≥50% or high tumor PD-L1 expression, based on the KEYNOTE-024 Phase III study (Reck et al 2016). Pembrolizumab also received accelerated approval in combination with platinum and pemetrexed in first line treatment-naïve non-squamous patients irrespective of PD-L1 status based on Phase II results in KEYNOTE-021 (Langer et al 2016) and confirmed in the Phase III KEYNOTE-189 study (Gandhi et al 2018). Recent results from CheckMate 227, a Phase III trial in patients with chemotherapy-naïve stage IV or recurrent NSCLC demonstrates improvement in PFS with first-line nivolumab plus ipilimumab than with chemotherapy among patients with a high tumor mutational burden (TMB), irrespective of PD-L1 expression level. (Hellmann et al 2018) supporting a potential role for the use of TMB as a selection marker for treatment. Furthermore, durvalumab was approved for patients with unresectable Stage III NSCLC based on Phase III results in the PACIFIC study (Antonia et al 2017).

2.2.2 Small Cell Lung Cancer Patients: Checkpoint Inhibitor Naïve

In 2012, the World Health Organization (WHO) estimated the worldwide incidence of new lung cancer cases was 1.8 million, resulting in approximately 1.6 million deaths and accounting for about 13% of total cancer diagnoses (Ferlay et al 2012). In the Western World, approximately 13% of the lung cancers that are diagnosed are small cell lung cancer (SCLC). SCLC occurs primarily in patients with a history of tobacco use and originates from neuroendocrine cell precursors. It is characterized by rapid growth, high response rates to both chemotherapy and radiotherapy, and the development of treatment resistance in patients with metastatic disease (Früh et al 2013).

Although SCLC is more responsive to chemotherapy and radiation therapy than other types of lung cancer, a cure is difficult to achieve because SCLC has a greater tendency to be widely disseminated by the time of diagnosis (NIH National Cancer Institute 2016). At the time of diagnosis, approximately 30% of patients with SCLC will have tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes. These patients are designated as having limited-stage disease (LD), where the treatment goal is curative (Früh et al 2013). Patients with tumors that have spread beyond the supraclavicular areas are said to have extensive-stage disease (ED). The prognosis of SCLC strongly depends on the tumor stage, which is evaluated by the new tumor-node-metastasis (TNM) version 7 staging system according to the Union for International Cancer Control (UICC) (Früh et al 2013).

In the last 30 years, multiple therapeutic agents and strategies, including dose intensification, have been explored, but with marginal improvement in PFS, and significant toxicity. The most important advances have improved the precision of radiation therapy and have introduced better supportive care measures, such as more effective antiemetic regimens.

The generally accepted standard for first-line systemic therapy is etoposide combined with either cisplatin or carboplatin. Initial objective response rates of 60 to 80% are seen in patients without substantive co-morbid conditions. However, almost all patients with ED and most patients with LD experience disease progression within months of completing first-line therapy.

There is only one approved therapy for SCLC that has progressed on a platinum and etoposide combination regimen: topotecan, a topoisomerase 1 inhibitor. Recurrent/refractory SCLC is substantially less responsive to therapy than primary disease. Response rates for topotecan are approximately 25% for relapses occurring at least 3 months after completion of first-line therapy, and as low as 3 to 6% for progressive disease occurring at the time of or shortly after completion of first-line therapy. Objective responses to a third line of chemotherapy are uncommon.

Recent data demonstrates activity of checkpoint inhibitors in the treatment of SCLC. Two agents, pembrolizumab and atezolizumab, have recently demonstrated activity in both the monotherapy setting in recurrent SCLC and in combination with platinum and etoposide in untreated patients (Chung et al 2018, Ott et al 2017, Horn et al 2018). Monotherapy pembrolizumab demonstrated an ORR of 18.7% in unselected but previously treated SCLC patients and an ORR of 33-35.7% in the PD-L1 positive population (Chung et al 2018, Ott et al 2017). Addition of atezolizumab to platinum chemotherapy as initial therapy has shown a 2 month improvement in overall survival (Horn et al 2018). Although these initial checkpoint inhibitors have demonstrated activity, SCLC remains a major cause of morbidity and mortality worldwide with a significant unmet need for new effective and safe treatments.

2.2.3 Melanoma Patients: Checkpoint Inhibitor Experienced

Ipiliumumab was the first checkpoint inhibitor approved for use in unresectable or metastatic melanoma based on significant improvement in overall survival shown in a pivotal randomized double-blind Phase III study (Hodi et al 2010). Subsequent to this, nivolumab was approved in advanced melanoma patients without *BRAF* mutation (Robert et al 2015). Pembrolizumab was approved for treatment of patients with advanced or unresectable melanoma who progressed after ipilimumab and/or *BRAF* therapy (Ribas et al 2015; Robert et al 2015).

The combination of ipilumumab and nivolumab has recently received approval in previously untreated patients with unresectable or metastatic melanoma (Robert et al 2015), although toxicity may be more prominent with the combination therapy. An analysis involving patients with a PD-L1 expression level of more or less than 1%, suggests that this biomarker may determine the best option for individual patients, as monotherapy may provide sufficient results in terms of survival with less toxicity (Larkin et al 2015; Wolchok et al 2017).

2.2.4 Esophageal Squamous Cell Carcinoma Patients: Checkpoint Inhibitor Naïve

Treatment in esophageal squamous cell carcinoma (ESCC) patients without distal metastases is aimed at a radical cure by methods appropriate for their stage of cancer. Meanwhile, for patients with distal metastases or those with a postoperative distant recurrence, combination therapy with platinum based chemotherapy and 5-FU (FP therapy) is recommended as the standard treatment. In the second-line setting, single-agent chemotherapy is an established option based on patient benefit-risk assessment (Lordick et al 2016, Muro et al 2019, National Comprehensive Cancer Network 2019, Kitagawa et al 2019). Although second-line treatments with docetaxel and paclitaxel are used for patients with advanced ESCC that has progressed after first-line chemotherapy, they are associated with hematological, gastrointestinal, and neurological toxicities (Jimenez et al 2011) and with poor long-term survival (Kato et al 2011, Muro et al 2004). More recently pembrolizumab has been approved for second-line therapy for ESCC, with PD-L1 expression levels by CPS of $\geq$ 10. Similarly, nivolumab has shown positive Phase III data in second-line ESCC independent of PD-L1 expression (Kato et al 2019) which has led to the approval of nivolumab for the treatment of patients with unresectable advanced or recurrent esophageal cancer that has progressed following chemotherapy in Japan.

2.2.5 Targeting PD-1 and TIM-3 Antigens

Although patients with advanced NSCLC and melanoma can benefit from CPI therapy, many patients will progress. Therefore, new agents are needed to increase the proportion of responding patients, and ultimately improve survival. Several hypotheses exist for mechanisms of acquired resistance, such as acquisition of mutations which make tumors less susceptible to T-cell mediated killing through a loss of interferon gamma (IFNγ) response elements or MHC Class I (Zaretsky et al 2016). PD-1 is a checkpoint inhibitor that identifies activated and/or exhausted T-cells including tumor infiltrating CD8+ T-cells that recognize mutated tumor antigens (neo-antigens) through their T-cell receptor (TCR). Up-regulation of additional inhibitory surface membrane immune checkpoint proteins has been described following anti-PD-1 treatment. TIM-3 represents one such molecule co-expressed with PD-1 and induced by PD-1 blockade. PD-1 and TIM-3 expression correlate with the degree of impairment of tumor infiltrating lymphocytes (TILs), effector functions and, consequentially, with a poor prognosis.

TIM-3 is an emerging checkpoint inhibitory molecule involved in the regulation of antitumor immunity that is expressed on T-cells and innate immune cells (e.g., macrophages, dendritic, and natural killer (NK) cells), where it has been shown to suppress their responses upon interaction with their ligands (Anderson et al 2016; Das et al 2017). Recently, the results of a Phase I study of TSR-022, an anti–TIM-3 mAb, were reported for patients with advanced solid tumors (Weiss et al 2017). Overall, TSR-022 monotherapy was well tolerated across multiple dose levels. Adverse events were manageable and consistent with the safety profiles of other CPIs.

The role of the co-expression of PD-1 and TIM-3 has been found on TILs in inflamed tumors with an ongoing antigen-specific immune response against the tumor, including melanoma and NSCLC (Gros et al 2014; Thommen et al 2015). PD-1 and TIM-3 can be found up-regulated upon treatment with T-cell BsAbs. In mouse models, combined targeting of the PD-1 and TIM-3 pathways has been shown to be more effective in controlling tumor growth of syngeneic mouse tumors than targeting either pathway alone (Sakuishi et al 2010). Similarly, during chronic viral infection, the dual blockade of PD-1 and TIM-3 enhanced the function of exhausted virus-specific CD8 T-cells (Jin et al 2010). Indeed, preclinical experiments in PD-1–resistant tumors and analysis of patient tumor samples showed that TIM-3 can act as a marker and seems to have a role in the mechanism to evade immune response to anti–PD-1/PD-L1 therapy (Koyama et al 2016). Nevertheless, despite evidence in the literature, the exact mechanism for how TIM-3 interferes with anti-tumor immune response and the interaction with its putative ligands (e.g., Galectin-9, CEACAM-1, HMGB1 or phosphatidylserine) is not fully understood.

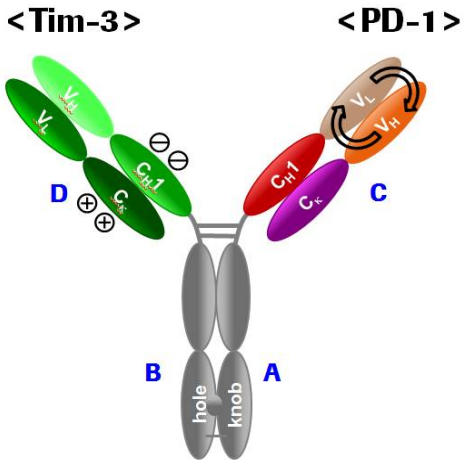
2.2.6 Description of RO7121661

RO7121661 is a novel, Fc-silent IgG1-based BsAb in the 1+1 format that incorporates monovalent binding to each of both checkpoint receptors, PD-1 and TIM-3. Use of a natural IgG-like monovalent heterodimeric IgG1 format allows avidity for simultaneous binding to PD-1 and TIM-3 when both receptors are co-expressed. RO7121661 binds with monovalent high affinity to a glycopeptide-epitope on PD-1, and with low affinity to TIM-3 to induce an avidity driven selectivity effect for binding to T-cells in the tumor microenvironment that co-express both PD-1 and TIM-3 or to T-cells expressing PD-1 alone. This preferential binding avoids the targeting of other TIM-3 expressing cells such as myeloid or NK cells.

An additional feature of RO7121661 is the specifically engineered IgG1-based Fc-region that prevents binding to FcγRs by introduction of PGLALA mutations (Kabat et al 1991; Schlothauer et al 2016). This may avoid tumor-associated macrophage resistance mechanisms, which have been observed with IgG4-based PD-1 antibodies such as pembrolizumab and nivolumab (Arlauckas et al 2017). A schematic of the antibody is shown in Figure 2.

A detailed description of the chemistry, pharmacology, and safety of RO7121661 is provided in the RO7121661 Investigator's Brochure (IB).

Figure 2 Schematic Representation of the RO7121661 Bispecific Antibody



Crossed PD-1 heavy chain (HC1 = A), crossed PD-1 light chain (LC1 = C), uncrossed TIM-3 light chain (LC = D), and TIM-3 heavy chain (HC2 = B). PD-1 = programmed death-1; TIM-3 = T-cell immunoglobulin and mucin domain 3.

2.3 BENEFIT/RISK ASSESSMENT

Benefit from cancer immunotherapy (CIT) with CPI mAbs, such as those targeting PD-1/PD-L1, is predominantly observed in a subset of patients with inflamed tumor phenotypes. However, response is not guaranteed even in this patient subset due to either primary or acquired resistance mechanisms. Upregulated TIM-3 expression on T-cells is associated with T-cell dysfunction potentially resulting in baseline or acquired resistance to anti-PD-1/PD-L1 therapies (Koyama et al 2016). Therefore, TIM-3 blockade may overcome or prevent resistance mechanisms to anti-PD-1/PD-L1 and help restore cytotoxic T-cell proliferation and enhance T-cell function. RO7121661, a novel IgG1-based BsAb that targets the CPI receptors PD-1 and TIM-3, may serve to overcome such resistance through ligand blockade and subsequent T-cell re-invigoration and/or potentially prevent or delay the development of resistance.

Compared to monospecific PD-1/PD-L1 directed antibodies, one might expect a similar safety profile, but better efficacy primarily coming from targeting both PD-1 and TIM-3 mediated immune resistance mechanisms. The reduction of drug internalization may also result in improved clinical pharmacology characteristics compared to monospecific antibodies. Compared to monospecific PD-1/PD-L1 and TIM-3 antibody combinations or other PD-1/TIM-3 bi-specifics, one anticipates similar efficacy in the context of better safety due to the preferential targeting of TILs, sparing of the myeloid compartment with avoidance of a peripheral sink, and lack of effector function due to the PGLALA mutation in the Fc region.

As the mechanisms for optimal targeting of immune regulation in the tumor environment are still under exploration, rational new approaches to increase response rates to first line CPI therapy are warranted. Untreated NSCLC patients who demonstrate TPS or PD-L1 $\geq$ 50%, which has clearly demonstrated sensitivity to PD-1 targeting, may benefit from first line treatment with a PD-1/TIM-3 BsAb if in fact the additional targeting of TIM-3 leads to additive antitumor activity beyond that expected of PD-1 targeting alone.

RO7121661 has demonstrated single-agent activity in Part A of this study. As of 1 March 2020, objective responses with long-lived partial remissions were achieved in one participant with metastatic ESCC and one participant with metastatic non-small cell lung adenocarcinoma. Of note, the non-small cell lung adenocarcinoma participant was previously treated with a PD-L1 inhibitor and had PD as best overall response on this treatment. Further, disease control with disease stabilization or minor response was achieved in other solid tumor types with an overall disease control rate (DCR) of 35.9% (14/39 patients).

RO7121661 was well tolerated in the patients dosed in Part A of this study. No specific safety concerns were identified and no MTD was identified although 1 DLT (Grade 3 Troponin T increased, unresolved at the time of the publication of this version of protocol) was observed at 1.2 g dose level.

Precaution against general risks for patients have been taken into account in the safety measures for this study, which include the definition of the inclusion/exclusion criteria (Section 5), dose-limiting toxicities (DLTs; Section 4.1.3), and rules for treatment interruption and withdrawal from study (Section 7).

The re-invigorating action of RO7121661 on immune effector cells, particularly given the TIM-3 modulation, might bear the risk of exaggerated immune cell activation that may result in the occurrence of enhanced, untoward, immune-mediated adverse events (imAEs) and an increase in cytokine release-mediated toxicities. Recommendations for the prophylaxis and the management of specific and known PD-1/PD-L1-mediated adverse events (AEs) can be found in Section 8.3.8 and Appendix 6.

Administration of therapeutic antibodies may cause infusion-related reactions (IRRs), which may include symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and vomiting. Such reactions typically occur during or shortly after the infusion, predominantly the first infusion. The incidence and severity typically decrease with subsequent infusions. Based on in vitro data, the risk of pro-inflammatory cytokine mediated IRRs upon first administration of RO7121661 as single agent is considered low. The recommended management of IRRs is detailed in Section 8.3.8.1.

Administration of therapeutic antibodies may cause the formation of ADAs, which may negatively affect the safety of the therapeutic (e.g., allergic reactions, immune

complex-mediated diseases). In the non-GLP DRF PK/PD study and the 4-week GLP study in cynomolgus monkeys, ADA development was observed independently of the dose groups (RO7121661 IB Section 4.2.2.1 and Section 4.2.3.1). No adverse findings were observed; no toxicity related to ADA formation was observed.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected adverse events of RO7121661 is provided in the RO7121661 IB.

Based on the considerations above, currently available data from Part A of this study and the planned safety monitoring and management guidance, the proposed study treatment is considered to have an appropriate benefit/risk profile for the population included in this study.

COVID-19 Benefit/Risk Assessment

In the setting of the coronavirus disease (COVID-19) pandemic, patients with comorbidities (including those with cancer) are a more vulnerable population. Infection with sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses. It is unclear how immunotherapy affects the incidence or severity of COVID-19. It is not anticipated that treatment with RO7121661 will increase the risk of infection with SARS-CoV-2. Severe COVID-19 is associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines IL-6, IL-10, IL-2, and interferon-gamma. RO7121661 has a low risk of CRS and, while it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a participant develops SARS CoV-2 infection while receiving RO7121661. At this time, there is insufficient evidence for causal association between RO7121661 and an increased risk of severe outcomes from COVID-19.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and SARS-CoV-2 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of SARS-CoV-2 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Cancer Comprehensive Network (NCCN) COVID-19 Vaccination Advisory Committee, SARS-CoV-2 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of SARS-CoV-2 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving RO7121661, a decision to administer the

vaccine to a patient should be made on an individual basis by the Investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving RO7121661 to receive SARS-CoV-2 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the Investigator when deciding on administering SARS-CoV-2 vaccines. When administered, SARS-CoV-2 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the SARS-CoV-2 vaccine is considered a concomitant medication and should be documented as such (see Section 6.5).

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints provided in Table 4, apply to:

- Part A: RO7121661 single agent dose escalation phase
- Part B: RO7121661 single agent expansion in selected indications

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• **Dose Escalation:** Safety, tolerability, MTD and/or RDE.	• Nature and frequency of DLTs and other AEs, PD and PK profile. • Incidence, nature and severity of AEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
• **Expansion:** Assessment of the anti-tumor activity of RO7121661.	• According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria: o Objective response rate (ORR). o Disease control rate (DCR); defined as ORR + stable disease rate (SDR). o Duration of response (DoR). o Progression free survival (PFS) defined as the time from the first study treatment (Day 1) to the first occurrence of progression per Investigator assessment or death from any cause, whichever occurs first.
Secondary	
• To characterize the immunogenicity profile of RO7121661 (Part A and B).	• Incidence of anti-drug antibodies (ADAs).
• To explore potential PD-1, TIM-3 and PD-1/TIM-3 specific PD biomarkers (Part B).	• Examine the profile and status of T cell proliferation/activation in tumor biopsies and peripheral blood.
• To investigate the single and multiple dose PK of RO7121661 (Part A and B).	• PK profiles and parameters derived for RO7121661.
• To explore degree of target binding of RO7121661 (in association with PK/PD) via RO (Part A).	• Evaluate RO via ex-vivo assay.
• To evaluate the safety and tolerability of RO7121661 (Part B).	• Incidence, nature and severity of AEs graded according to the NCI CTCAE v5.0.
• To explore preliminary anti-tumor activity of RO7121661 (Part A).	• According to RECIST Version 1.1 criteria: – Objective response rate (ORR). – Disease control rate (DCR). – Progression-free survival (PFS). – Duration of response (DoR).

Table 4 Objectives and Endpoints (cont.)

Objectives	Endpoints
Tertiary/Exploratory	
• To make a preliminary assessment of the anti-tumor activity of RO7121661 using immune-related RECIST (iRECIST) (Part A and B).	• Investigator-determined assessment using iRECIST: o ORR. o DCR; defined as response rate (RR) + stable disease (SD). o DoR. o PFS defined as the time from the first study treatment (Day 1) to the first occurrence of progression per Investigator assessment or death from any cause, whichever occurs first.
• To make a preliminary assessment of overall survival from RO7121661 (Part A and B).	• Overall survival (OS), defined as the time from first study treatment to death from any cause (if data mature at the time of analysis).
• To explore and identify potential PD biomarkers in association with exposure kinetics (Part A and B).	• Examine PD changes in the following compartments: o Tumor Microenvironment (pre– and on-treatment tumor biopsies): Measure changes in degree and extent of T-cell infiltration and inflammatory gene expression profiles/signatures. o Peripheral Blood: Serial sampling to assess kinetic changes in select T-cell subsets, inflammatory cytokines, soluble factors, gene signatures and monitoring tumor burden.
• Correlation of anti-tumor activity of RO7121661 to PK, PD and safety (Part A and B).	• Compare anti-tumor activity by RECIST with PK parameters, PD changes and safety events.

ADAs = anti-drug antibodies; AEs = adverse events; ctDNA = circulating tumor DNA; DCR = Disease control rate; DLTs = dose-limiting toxicities; DoR = Duration of response; iRECIST = immune-related RECIST; IV = intravenous; MTD = maximum-tolerated dose; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; ORR = Objective response rate; OS = Overall survival; PD = pharmacodynamics; PFS = Progression free survival; PK = pharmacokinetic; RDE = recommended dose for expansion; RECIST = Response Evaluation Criteria in Solid Tumors; RO = receptor occupancy; RR = response rate; SD = stable disease; SDR = stable disease rate; TMB = tumor mutational burden.

4. STUDY DESIGN

4.1 OVERALL DESIGN

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

Study NP40435 is a first-in-human, open-label, multicenter, Phase I multiple-ascending dose (MAD) study of single agent RO7121661. The study consists of 2 parts (A and B):

- **Part A** (RO7121661 Dose Escalation): To determine the MTD and/or RDE based on safety, tolerability, PK, and/or the PD profile of escalating doses of RO7121661 every 2 weeks (Q2W). If for specific cleared cohort(s) the safety, PK and/or RO and/or the biomarker profile need to be further characterized, additional participants, potentially enriched in certain indications and/or characteristics, may be enrolled.
- **Part B** (RO7121661 Tumor-Specific Expansion Cohorts): To evaluate anti-tumor activity of the RDE of RO7121661 from Part A (2.1 g Q2W) and to confirm safety and tolerability in participants with selected tumor types. B1, B2, B4 and B5 expansions may be staggered, sequential or concurrent. Part B3 will not proceed prior to generation of data from the initial CPI experienced indication(s):
  - **Part B1:** CPI experienced second line and beyond metastatic melanoma
  - **Part B2:** CPI and platinum experienced second or third line PD-L1 positive NSCLC
  - **Part B3:** PD-L1 positive, CPI naïve, first line NSCLC
  - **Part B4:** CPI-naïve SCLC with prior failure of, progression on, or intolerance to standard therapy
  - **Part B5:** CPI-naïve ESCC

Part A of the study will enroll participants with solid tumors who have progressed on a cancer therapy or who are not amenable to standard of care. At least [redacted] DLT evaluable participants will be enrolled in each cohort during the dose escalation (see Section 4.1.3). Dose escalation will be carried out according to a modified continual reassessment method (mCRM) with escalation with overdose control (EWOC) design, with the aim of identifying the MTD/RDE of RO7121661.

Since RO7121661 will be administered Q2W in Part A, the cycle length will be defined as 14 days. The maximum total number of participants in the dose escalation portions of Part A1 will be approximately [redacted] DLT evaluable participants on a Q2W schedule. A dose cohort can be extended to enroll additional participants (approximately [redacted]), potentially enriched in certain tumor types and/or characteristics to confirm safety, PK and/or RO and/or the biomarker profile.

Part B1 and/or B2 and/or B4 and/or B5 may commence upon completion of Part A. The starting dose of RO7121661 for Part B is 2.1 g Q2W as derived from the RDE in Part A

determined by safety, PK and/or RO and/or the biomarker profile. Part B3 will not proceed prior to generation of data from the initial CPI experienced indication(s).

Patients enrolled in Part B expansions have more specific limitations of prior therapies for inclusion than during the dose escalation. Patients enrolled in Part B1 (CPI experienced melanoma) must have had treatment with approved anti-PD-L1/anti-PD-1 checkpoint inhibitors. Patients enrolled in Part B2 (CPI and platinum experienced, PD-L1 expression ≥ 1% NSCLC) must have had a checkpoint inhibitor and platinum chemotherapy. Patients enrolled in Part B3 (untreated, CIT naïve NSCLC with PD-L1 expression ≥ 50%) should not have had any prior therapy. Patients enrolled in Part B4 (CPI naïve SCLC) and B5 (CPI-naïve ESCC) should not have had any prior checkpoint inhibitor therapy but may have had chemotherapy. Specific details for Part B Expansions are included in the Inclusion and Exclusion Criteria (Section 5.1 and Section 5.2).

In Part B (tumor specific expansion cohorts) approximately [redacted] participants will be included per indication. Part B cohorts may run in parallel, staggered or sequentially.

Participants will be treated with RO7121661 until disease progression, unacceptable toxicities, or withdrawal of consent. Participants may continue treatment with RO7121661 (Part A and B) for 24 months *or longer if the participant is still benefitting from treatment at the time of the last visit at the end of the two-year period*. As with other immunotherapies, treatment beyond progressive disease according to RECIST Version 1.1 can be considered after consultation and agreement between the Sponsor and Investigator.

4.1.1 Length of the Study

The duration of the study for each participant will be up to 27 months (Parts A and B), divided as follows:

- 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 (± 7) days after last treatment with RO7121661 for Part A; 90 (± 7) days after last treatment with RO7121661 for Part B.
- Survival follow-up: 90 (±7) days after last treatment with RO7121661; then every 3 months (± 2 weeks) for total 24-month period after initial dose.

The treatment period may be prolonged past month 24 if the participant is still benefitting from treatment at the time of the last visit at the end of the two-year period. Participants may extend treatment within the ongoing study whether they are on treatment or are on a treatment pause at the 24-month time point. During the extended treatment period, the participant follows the SoA as indicated for "Subsequent Cycles." Participants will be treated until disease progression, unacceptable toxicities, or

withdrawal of consent. For participants who extend their treatment, the safety follow-up will be performed 60 (± 7) days for Part A or 90 (± 7) days for Part B after the last treatment with RO7121661 and survival follow-up every 3 months (± 2 weeks) thereafter for a total of 48 months after initial dose, or end of the study.

4.1.2 Dose-Escalation Decision Criteria

For Part A, RO7121661 dose-escalation will be carried out according to a mCRM with EWOC design and will be based on the occurrence of DLTs. The dose-toxicity relationship is described by a 2-parameter logistic regression model, where the probability of DLT is expressed as a function of dose. The model is continuously updated as additional participant information becomes available (for further information see Appendix 10).

A minimum of [redacted] participants per cohort will be enrolled and treated in a sequential manner with one week between the first and second participant and at least 2 days between subsequent participants. However, if the first participant experiences a DLT within the first week, then the time between the treatment of subsequent participants within the same cohort may be increased.

A new cohort can be opened when at least [redacted] participants per cohort are considered DLT evaluable, i.e., if they received 2 doses and either:

- experienced a DLT within the DLT period
- cleared the DLT period without a DLT

The DLT period is 21 days from Day 1/Cycle 1 to Day 7/Cycle 2. If there is a delay in Cycle 2 treatment the DLT period should be adjusted to cover Day 7/Cycle 2 up to a maximum of 35 days, since the maximum dose delay allowed is 14 days.

Once at least [redacted] participants per cohort are DLT-evaluable, the logistic regression model will be updated with the treatment outcome (i.e., the occurrence of DLT). Thus, a new estimate of the MTD (defined as the dose with the highest probability that the DLT rate is within the target of 20-35% and a relatively low probability $<25\%$ that the DLT rate is above 35%) will be derived. In addition, the model will recommend a dose for the new cohort of participants, with the EWOC recommendation being either the new estimate of the MTD or the highest allowable dose based on pre-specified safety constraints (e.g., maximum increments), whichever is lower.

Built in safety constraints are in place to prevent exposing participants to undue risk of toxicity. For instance, in the absence of DLT, the maximum allowable dose-increment will be 200% (i.e., next dose could be as high as 3-fold the previous dose) for dose-levels <700 mg and 100% (i.e. 2-fold) for dose-levels ≥ 700 mg. In addition, in case of one event meeting DLT criteria in a dose-level, the maximum allowable dose

increment becomes 100% (i.e. 2-fold); while in the presence of 2 DLTs an increment of 50% is allowed (i.e. 1.5-fold). For further information see Table 1 in Appendix 10.

The dose escalation decision and selection of the dose for the next cohort, guided by the mCRM EWOC recommendation, will also take into account an overall review of safety and available PK and/or PD data as well as any additional data. Subject to clinical judgment, and upon agreement between the Sponsor and the Investigators on the next dose-escalation step, the new cohort can then be opened for enrollment.

The design will continue as described, until one of the pre-defined stopping criteria is satisfied (see Section 4.1.4), or the RDE has been defined, whichever comes first.

4.1.3 Dose Limiting Toxicities

For the purpose of this study, a DLT will be defined as any of the following events attributed to RO7121661 (i.e., related to RO7121661) and occurring during the DLT window:

A DLT is defined as a clinically significant AE (classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.5.0, as applicable) or significant laboratory abnormality: 1) occurring during the DLT assessment period of 21 days from the start of the first RO7121661 administration; 2) considered to be related to study treatment RO7121661 by the Investigator and; 3) is not attributed to disease progression or another clearly identifiable cause.

Investigators are encouraged to perform additional tests to determine the underlying etiology and most appropriate attribution.

For the purpose of this study the following AEs are considered DLTs:

- Hematological toxicities:
  - Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) lasting > 5 days.
  - Grade ≥ 3 febrile neutropenia associated with single body temperature > 38.3°C or sustained body temperature ≥ 38°C for > 1 hour, and/or with infection.
  - Grade 4 thrombocytopenia lasting > 48 hours.
  - Grade 3 thrombocytopenia associated with bleeding episodes requiring a platelet transfusion.
  - Grade 4 anemia
  - Grade ≥ 3 anemia with hemolysis
- Any non-hematological toxicity of Grade ≥ 3 including:
  - Any Grade 3 immune-mediated AE.
  - Grade 3 hyperbilirubinemia lasting for > 48 hours or Grade 4 hyperbilirubinemia.

- Grade ≥ 3 AST or ALT elevations with hyperbilirubinemia of Grade ≥ 2.
- Grade 4 AST or ALT elevations.
- Grade ≥ 3 nausea, vomiting, or diarrhea despite maximal supportive treatment.
- Grade ≥ 3 non-hematological laboratory abnormality requiring medical treatment/intervention or hospitalization.

- The following Grade ≥ 3 non-hematological toxicity are **exceptions** for consideration as DLTs:
  - Alopecia (any grade).
  - Grade 3 nausea or vomiting that resolves to Grade ≤ 1 with or without supportive therapy within one week.
  - Grade 3 hypophosphatemia resolved within one week.
  - Grade ≥3 fatigue/asthenia that resolves to Grade ≤ 2 within one week.
  - Grade 3 anorexia or constipation.
  - IRRs are not considered to be DLTs because, on the basis of experience with mAbs, IRRs are not dose-related events. Hence, IRRs that require removal of participants from the study will be considered as treatment limiting toxicities and not DLTs. Precautions, including pre-medication, will be taken if IRRs of Grade ≥ 2 occur. If described precautions are not sufficient, other options will be discussed between the Sponsor and the Investigator (see Section 8.3.8.1). However, re-occurrence of an IRR event in a participant that precluded the administration of the full dose or the administration of the next scheduled dose of study drug will be considered a DLT. If clinical judgment suggests that an IRR is related to dose (e.g., driven by on-target mediated release of cytokines by immune cells), a Grade 3 or Grade 4 IRR may be considered a DLT.
  - Grade 3 fever (in the absence of any clinically significant source of fever) that resolves to Grade ≤ 2 within 7 days with supportive care.
  - Fever > 40°C (i.e., Grade 3) that occurs within 48 hours of RO7121661 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 is asymptomatic and 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 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

- Grade 3 neuropathy if the participant began therapy with a Grade 2 neuropathy at baseline.
- Grade 3 hypoxia that starts within 24 hours of infusion and improves/resolves to Grade $\leq$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 RO7121661-related toxicity that results in a dose-delay of the next scheduled administration of more than 14 days is defined as a DLT.

4.1.4 Stopping Rules Criteria

4.1.4.1 Part A Dose Escalation

The algorithm of the mCRM with EWOC will propose to stop the dose escalation under the following circumstances:

- The maximum sample size of [redacted] evaluable participants has been reached **OR**
- Enough information on MTD has been achieved (i.e., at least a minimum of [redacted] participants enrolled *and* at least [redacted] participants have been accrued near the MTD dose - where near is defined as differing from the MTD by at most 15% - *and* the probability that the MTD dose lies within the target toxicity interval is above 50%)

  OR

- The maximum dose has been tested and is considered safe (i.e., at least a minimum of [redacted] participants have been accrued at the maximum dose or near - differing from the maximum dose by at most 5% - *and* it is at least 50% likely that the probability of a DLT for that maximum dose is below 20%).

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

For Part A: Upon completion of all screening evaluations and confirmation that a participant has met all inclusion and exclusion criteria, investigator sites will contact the Sponsor to confirm the dose, participant number and cohort assignment via a Confirmation of Enrollment form (ESF). This will guarantee that the Sponsor is notified

prior to the administration of RO7121661 to any participant. Then sites will need to contact the interactive response technology system (IRT) vendor who will generate confirmation of participant number, dose and cohort assignment. The IRT participant number should be generated prior to first dose.

For Part B: An Interactive Response Technology (IRT) system will be utilized to manage (pre-) screening and enrollment. All pre-screening evaluations must be recorded in the IRT system with a proposed cohort. Roche will review and approve the pre-screened participants for the proposed cohort. After signing informed consent, the screening transaction should be performed in the IRT system and once it is confirmed that participants meet all eligibility criteria the participants should be enrolled in the respective cohort using the IRT system.

A participant Enrollment List must be maintained by the Investigator.

In Part A: After each participant receives RO7121661 the Investigator(s) must confirm to the Sponsor that the participant has been dosed and provide a brief summary of the status of the participant in terms of safety and tolerability to RO7121661. The Investigators and the Sponsor will communicate regularly and on an ad-hoc basis to discuss the occurrence of any safety events including DLTs.

In the event of a DLT, the Investigator will contact the Sponsor immediately (within 1 business day via DLT notification form) to discuss participant status and action taken/to be taken.

In addition, as outlined above, during dose-escalation, after each participant cohort has been completed (i.e., at least [redacted] participants are DLT evaluable), the Sponsor will organize a teleconference with the Investigators to discuss the safety and tolerability of RO7121661 and to discuss the proposed dose(s) for the next cohort. The dose-escalation decision criteria are outlined in Section 4.1.2.

During these teleconferences, NCI CTCAE Version 5.0 toxicities will be discussed along with the results of any available PK/PD data, in addition to safety laboratory results and any other available data that may assist the dose-escalation decision process. The decision will be based on all relevant available data and not based solely on DLT information, as well as being guided by the mCRM-EWOC recommendation.

Study Investigators and the Sponsor should reach a consensus on the next dose-level which may include dose escalation, de-escalation, or recruitment into the current or particular previously cleared cohorts. Dose-escalation may proceed to the next dose level if the Investigators and the Sponsor are satisfied with the safety profile of the previous participant cohort and agree to move to the next escalated dose level or whether to de-escalate and/or extend recruitment into particular cohorts. The dose discussion will be documented in writing, including the final dose decision whether it is

the mCRM recommended dose, or an intermediate dose, and both the Sponsor and Investigators will approve the Minutes of these meetings to confirm agreement.

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

4.2 JOINT MONITORING COMMITTEE

In Part B of the study, the Sponsor will in addition form a Joint Monitoring Committee (JMC), with the aim to monitor participants' safety throughout. The JMC will consist of designated Sponsor personnel, including a JMC Chair, clinical scientist, drug safety officer, biostatistician, and independent clinical expert(s) (i.e., expert[s] independent from the Sponsor).

The JMC will conduct regular assessments on an ongoing basis of the incidence and nature of AEs, serious adverse events (SAEs), adverse events of special interest (AESI), frequency of death from all causes, and clinically significant laboratory abnormalities. The JMC will review all safety study data at regular intervals, as defined in the JMC charter.

At the time of each review, the JMC will make one of the following recommendations: the study may continue unchanged, the study is to be stopped, additional analyses are to be performed, enrollment is to be held pending further safety evaluations, or a protocol amendment is recommended. The JMC will report recommendations to the Sponsor.

4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

For Part A, RO7121661 dose escalation will be carried out according to a mCRM with EWOC design and will be based on the occurrence of DLTs.

The mCRM EWOC design has many favorable characteristics:

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

participants to overly toxic doses. Of note, the model provides only the upper limit for recommended dose. A dose less than the model recommended dose may be selected based on clinical judgment.

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 parameters of the design as implemented for this study (Appendix 10).

For Part B, RO7121661 will be administered at the determined MTD/RDE to specific participant populations in expansion cohorts. From the data available from Part A, a dosing regimen of 2.1 g Q2W was selected as the dose for Part B expansion cohorts. Please refer to Section 4.4 for further rationale.

4.3.1 Rationale for Study Population

Part A dose-escalation of this study will enroll participants with advanced and/or metastatic solid tumors who have progressed on a cancer therapy or for whom no effective standard therapy exists. In the event that additional data is required to confirm PK, PD, safety, etc., additional participants, potentially enriched in certain tumor types and/or characteristics, may be enrolled.

Part B of this study will enroll melanoma patients who have progressed on prior CPI (B1) or NSCLC patients who are CPI and platinum chemotherapy experienced (B2) and CPI naïve SCLC (B4) and ESCC patients (B5). If exploration is supported by CPI experienced patients in Parts B1 and/or B2, then Part B of this study will also enroll NSCLC patients who are CIT and chemotherapy naïve (B3). SCLC and ESCC patients who are CPI naïve may enroll without data from B1 or B2.

Data from PD-1/PD-L1 inhibitors which are approved or in development as described in Section 2.2, have demonstrated clinical benefit in the NSCLC and melanoma populations. Therefore, CPI experienced populations allow for an assessment of the combination of PD-1 and TIM-3 targeting with the potential of providing participants an opportunity for therapeutic benefit if continued PD-1 targeting in combination with targeting TIM-3 can help re-initiate or improve on the anti-PD-1/PD-L1 CPI response.

Recent data from PD-1/PD-L1 inhibitors demonstrate benefit in both the previously treated and untreated SCLC population (see Section 2.2.2). In addition, there is early but limited data suggesting potential activity of a monospecific TIM-3 antibody in SCLC, thus suggesting a potential role of TIM-3 (Harding et al 2019).

Additionally, CPI naïve ESCC patients who are refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs (B3) will be enrolled. Recent

data from PD-1 inhibitors demonstrate benefit in the ESCC population (see Section 2.2.4). Compared to esophageal adenocarcinoma PD-L1 expression is enriched in ESCC, which might increase tumor susceptibility in these patients to elimination following immune checkpoint inhibition. The reported prevalence of PD-L1 expression in ESCC ranges from 15% to 83% in tumor cells, and from 13% to 31% in tumor-infiltrated immune cells (Jiang et al 2017, Lam et al 2017,.Guo et al 2018, Qu et al 2016). TIM-3 has also been shown to be expressed on TILs in patients with ESCC (Zhao et al. 2020). RO7247669 may therefore have the potential to be a therapeutic option for patients with ESCC.

For CIT naïve previously untreated NSCLC patients, focus will be on those participants with at least ≥ 50% PD-L1 expression as based on pembrolizumab study KEYNOTE-024 (Reck et al 2016), as these are participants felt to have the highest opportunity for response to PD-1 therapy and therefore may gain additive activity from the TIM-3 mechanism of the BsAb.

Other indications may be explored in the tumor-specific expansion cohorts in Part B based on emerging clinical data from the Part A dose-escalation and/or based on emerging scientific rationale. These additional indications may be proposed and added to this study for Part B via an amendment.

4.3.2 Rationale for Biomarker Assessments

Biomarker exploration will focus on PD effects associated with anti-PD-1/TIM-3 therapy. A driving hypothesis is that PD-1/TIM-3 dual blockade will increase T-cell infiltration and proliferation in the tumor microenvironment provided sufficient RO (or drug coverage) is obtained.

Fresh tumor biopsies will be collected according to the SoA (see Section 1.3), to measure changes in the degree and extent of T-cell infiltration (such as CD8/Ki67) and select inflammatory gene expression profiles/signatures.

In peripheral blood, serial blood sampling will be done to assess kinetic changes in drug RO, immune cellular profiles and selected cytokines. The analysis of cytokines during study treatment has demonstrated increases of interleukin (IL)-6, IL-8, and IFNγ in previous CPI trials and might serve as markers of the mode-of-action. These cytokines may also be important in the context of drug safety and might therefore be analyzed in the case of (severe) AEs. Furthermore, soluble CD25, which has been described as a circulating marker of IL-2 mediated immune cell activation (Ribas et al 2009) may be measured at baseline and selected time points after initial treatment. Additionally, peripheral blood will be collected to assess kinetic changes, such as TMB and potentially circulating tumor DNA (ctDNA).

Whether predictive markers of response to therapy exist for RO7121661 and for which cancer type or clinical settings will also be explored. The hypothesis that PD-1/TIM-3

dual blockade might be most effective in settings where there is a composite profile consisting of but not limited to T-cell infiltration/activation, PD-L1 status, PD-1 and TIM-3 target expression, and TMB, will be explored in baseline tumor biopsies.

Archival tumor tissue biopsies will be collected from all participants if available. Archival samples will be tested for similar predictive markers that the fresh screening biopsies will be tested for.

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

4.4 DOSE JUSTIFICATION

Part A

The starting dose regimen of RO7121661 will be 70 mg administered Q2W by IV administration in this first study in humans with RO7121661. The RO7121661 starting dose and schedule have been selected on the basis of the integration of several factors including non-clinical toxicology, PK and in-vitro/ex-vivo functional assays.

RO7121661 was well tolerated in both the dose range finding and GLP monkey toxicology studies up to the highest dose evaluated (150 mg/kg). Toxicology findings were consistent with reported findings in cynomolgus monkey studies with marketed CPIs.

The safety profile of the proposed Q2W dosing regimen for RO7121661 administration in human has been supported by a more frequent dosing (QW schedule) in non-clinical toxicology studies conducted in cynomolgous monkeys. The entry-into-human starting dose of 70 mg Q2W (corresponding to a 1 mg/kg Q2W in an average 70-kg–weight participant) for the dose-escalation portion of this study was derived from a translational PK/PD approach, which was informed by in vitro and ex vivo staphylococcal enterotoxin B superantigen-induced (SEB) cytokine release assays as well as clinical safety experience with pembrolizumab, nivolumab (anti–PD-1), other PD-1/PD-L1 inhibitors, and TSR-022, a mAb directed against the TIM-3 receptor. Since there are extensive clinical (safety) data available from PD-1 inhibitors, a non-MABEL (minimum anticipated biological effect level) approach using PK/PD was considered appropriate to estimate a safe starting dose. The PK/PD approach is expected to reduce the number of participants exposed to sub-pharmacological doses of RO7121661 while ensuring that the starting dose is in a safe range. The projected area under the curve $(AUC)_{0\text{-}336}$ and maximum concentration (C_{max}) in humans at the flat dose of 70 mg after single dose (Q2W) are 3900 µg • h/mL and 25.2 µg/mL, respectively. These values are approximately 180- and 116-fold lower, respectively, than the exposure observed in cynomolgus monkeys at the 150 mg/kg NOAEL in the 4-week GLP toxicology study (differences in potency and dosing schedule were accounted for). For further information

on exposure ratios from non-clinical safety findings to human exposures for single administration and steady state, see Appendix 11.

Human PK simulation via allometric scaling of the linear clearance data from cynomolgus monkey is consistent with an IgG-like PK, with a projected human half-life of ~19 days at target-mediated drug disposition (TMDD)-saturated doses. At lower doses, RO7121661 is predicted to show a more rapid clearance due to TMDD.

The safe starting dose is predicted to show a maximal response in an ex vivo SEB cytokine release assay up to 70% (with unknown TIM-3 contribution) which should result in pharmacological activity in participants. To support comparison of these functional assays, pembrolizumab, another PD-1 inhibitor currently on the market where tolerable doses (no DLT observed) up to 10 mg/kg Q2W were investigated, was included for benchmarking. The starting dose selected for pembrolizumab was 1 mg/kg and showed full saturation in target engagement in these assays (Patnaik et al 2015).

Compared to a classical MABEL approach, the approach used here reduces the number of participants exposed to sub-therapeutic doses of RO7121661 while ensuring that the starting-dose is in a safe range.

The initially proposed Q2W dosing interval is supported by the predicted clearance and elimination half-life ($t_{1/2}$) of RO7121661 with a projected human elimination $t_{1/2}$ of approximately 19 days.

A maximum feasible dose of 2.1 g of RO7121661 has been defined based on predicted IC_{95} for PD-1/TIM-3 of approximately 320 μg/mL and confidence in ex vivo and in vitro SEB data and benchmarking results to pembrolizumab. Based on product specifications, the dosing is currently limited to 2.1 g and must not be exceeded under any circumstances. In case dose escalation is planned to progress beyond 2.1 g, the corresponding chemistry, manufacturing, control (CMC) documents and protocol will be amended as appropriate.

Flat dosing was selected for this protocol because no strong influence of body surface area (BSA) or body weight on overall exposure is expected. On the basis of the PK data emerging from this clinical study, any potential covariates on exposure to RO7121661, such as BSA, body weight, age, ethnicity and gender will be explored in order to confirm this dosing approach.

In conclusion, a 70 mg flat dose is proposed as the starting dose of RO7121661 for Part A, on the basis of both data from nonclinical studies with RO7121661 and previous clinical experiences with PD-1/PD-L1 and TIM-3 inhibitors.

Part B

From the data available from Part A of this study, a dosing regimen of 2.1 g Q2W was selected as the dose for Part B expansion cohorts. This was based on RO7121661 being well tolerated in the patients dosed in Part A where no specific safety concern associated with RO7121661 was identified. One DLT (Grade 3 Troponin T increased) was observed at the 1200 mg dose group, however no MTD was identified.

A two compartmental PK linear model predicts the exposure data well, particularly at the higher dose range and supports a dose of 2.1 g at Q2W for further investigation. A dose regimen of 2.1 mg QW is predicted to result in a trough concentration of >320 µg/mL, the predicted EC95 from an ex vivo SEB cytokine assay, in 62% of patients. The dose and regimen may be optimized based on ongoing exposure-response analysis.

The supporting data for the RDE from Part A can be found in the current RO7121661 Investigator's Brochure.

4.5 END OF STUDY DEFINITION

The end of the study is defined as the last participant's last visit (LPLV) per protocol (includes the safety follow-up visit 60 days (Part A) or 90 days (Part B) after last dose of study drug) or the date at which the last data point from the last participant required for statistical analysis is received (last participant, last observation), whichever is the latest date. Because of the exploratory nature of this clinical study, any part of 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 4.3.1.

The study population consists of male and female participants with advanced and/or metastatic solid tumors.

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

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

5.1 INCLUSION CRITERIA

General Inclusion Criteria for Parts A and B

Participants are eligible to be included in the study only if all of the following criteria apply prior to dosing on Cycle 1, Day 1.

Informed Consent

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

Age

2. Age $\geq$ 18 years.

Type of Participants and Disease Characteristics

3. For Part A only: Patients with advanced and/or metastatic solid tumors who have progressed on a cancer therapy, for whom no effective standard therapy exists, or who decline treatment with approved therapies.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 and a life expectancy of $\geq$ 12 weeks.
5. Adequate cardiovascular function:
    - New York Heart Association (NYHA) Heart Failure Stage ≤ 2.
    - Baseline-corrected QT (QTcF) interval ≤ 470 ms.
    - Resting systolic blood pressure ≤ 150 mmHg and diastolic blood pressure 100 mmHg (average of ≥ 3 readings on $\geq$ 2 sessions with short break between sessions) (no clinically significant hypertension).
    - Resting heart rate (HR) between 45-100 bpm (no clinically significant tachycardia).
6. Adverse events from any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade $\leq$ 1, except alopecia (any grade), vitiligo, endocrinopathy managed with replacement therapy and Grade 2 peripheral neuropathy.
7. Adequate hematological function: neutrophil count of $\geq 1.5 \times 10^9$ cells/L (1500/μl), platelet count of $\geq 100 \times 10^9$/L (100,000/μL), hemoglobin ≥ 9 g/dL (90 g/L), lymphocyte count of $\geq 0.5 \times 10^9$ cells/L (500/μL).
    - Hemoglobin must be stable for at least a week without need for packed red blood cell transfusion.
8. Adequate liver function: total bilirubin $\leq 1.5 \times$ ULN; aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase $\leq 2.5 \times$ ULN; with the following exceptions:
    - Participants with known Gilbert disease or hepatocellular carcinoma: serum bilirubin level $\leq 3 \times$ ULN.
    - Participants with documented liver metastases: AST and ALT $\leq 5 \times$ ULN.
    - Participants with documented liver or bone metastases: ALP $\leq 5 \times$ ULN.

9. Adequate renal function: serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance by Cockcroft-Gault formula ≥ 50 mL/min for participants in whom, in the Investigator's judgment, serum creatinine levels do not adequately reflect renal function. Cockcroft-Gault glomerular filtration rate estimation:

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

10. Additional adequate laboratory parameters:
    - Serum albumin ≥ 25 g/L (2.5 g/dL).
    - For participants not receiving therapeutic anticoagulation: Prothrombin time (PT) and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN or $< 2 \times$ ULN for participants with HCC.
    - For participants receiving therapeutic anticoagulation: stable anticoagulant regimen.
11. Negative HIV test at screening.
12. Negative hepatitis B surface antigen (HBsAg) test at screening.
13. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening.
    - The HBV DNA test will be performed only for participants who have a positive total HBcAb test.
14. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening.
    - The HCV RNA test will be performed only for participants who have a positive HCV antibody test.
15. Diagnosis of locally advanced and/or metastatic solid tumors with radiologically measurable disease according to RECIST v1.1.
    - Previously irradiated lesions should not be counted as target lesions unless clearly progressed after the radiotherapy.
    - Participants must have at least one measurable lesion (target lesion [TL]) not intended to be biopsied.
    - Lesions that are intended to be biopsied should not be counted as target lesions.

Contraception

16. Male and/or female participants

    The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic

abstinence (e.g., calendar, ovulation, symptom-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

a) Female Participants

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

- Not a woman of childbearing potential (WOCBP, as defined in Section 1 of Appendix 5).
- WOCBP, who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 4 months after the final dose of RO7121661.
  - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices (see Appendix 5).
  - Have a negative pregnancy test (blood) within the 7 days prior to the first study RO7121661 administration.

b) Male Participants

During the treatment period and for at least 4 months after the final dose of RO7121661, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year, with partners who are women of childbearing potential (WOCBP, as defined in Section 1 of Appendix 5).

  With pregnant female partners, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
- Refrain from donating sperm during this period.

Specific Inclusion Criteria for Biopsies

17. Participants who are enrolled on the parts of the study where fresh biopsies are requested (i.e. biomarker cohort(s) and expansion cohorts B1, B2, B3, B4 and B5) must have at least one non-target tumor lesion accessible to biopsy per clinical judgment of the treating physician and consent to undergo mandatory fresh baseline and on-treatment biopsy. Participants in Part B, presenting with only one target lesion and no non-target lesions that can be biopsied may omit mandatory biopsies. *In such cases, the Medical Monitor is available to the Investigator to advise and answer any questions in this regard*. A lesion with evidence of progression by imaging (or measurement for cutaneous lesions) is preferred if it can be assessed

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

Specific Inclusion Criteria for Part B Expansion in CPI Experienced Patients

CPI experienced patients are defined in this study as those who have had prior treatment with an anti-PD-1 or anti-PD-L1 agent. Participants must meet the following additional criteria to be eligible for inclusion in Part B of the study if they are CPI experienced.

18. Participants with advanced and/or metastatic malignancies who have progressed on an anti-PD-L1/ anti-PD-1 agent.
19. Participants who are considered to be deriving benefit from treatment post progression, as per clinical judgment, are not considered eligible. Screening tumor assessment should confirm progression.
20. Prior anti-PD-L1/PD-1 as monotherapy and/or as combination therapy may have been administered as indicated for the respective indications, with the exception of adjuvant therapy.

Melanoma Cohort (CPI-Experienced; Part B1)

21. Participants with histologically confirmed advanced metastatic melanoma previously treated with approved anti-PD-L1/anti-PD-1 agents with or without approved anti-CTLA-4 therapy and up to one additional treatment regimen
    - Eligibility of participants receiving previous treatment with non-approved anti PD-1 or anti-PD-L1 inhibitors or combination treatment with other non-approved agent(s) *may be discussed with* the Medical Monitor prior to enrollment. *The decision to enroll the patient in the study is the responsibility of the Investigator.*
22. Participants whose tumors have a known BRAFV600 mutation must also have experienced disease progression (during or after treatment) or intolerance with BRAF inhibitor(s) and/or MEK inhibitor(s) if treatment is available. Participants with BRAFV600 mutation but refusing such inhibitor(s), or not available to them, will be eligible.
23. Enrollment will be managed so that:
    - No more than approximately 10% of participants in this cohort will be participants with ocular (uveal) melanoma.
    - Up to 10 patients with primary resistance to CPI will initially be enrolled. This may be expanded if efficacy and or biomarker assessments for proof of mechanism warrant further exploration.
        - Primary resistance is defined as Investigator assessed best overall response of progressive disease within the first 10 weeks of anti-PD-L1/anti-PD-1 treatment.
            - If a scan within the first 10 weeks exists and shows progressive disease the patient is considered primary resistant (i.e. the scan

result cannot be overruled by investigator assessment of clinical benefit).

- Should a subsequent scan for the same line of treatment show clinical benefit after initial radiographic progression (i.e. pseudoprogression) the patient is not considered primary resistant.

NSCLC Cohort (CPI-Experienced; Part B2)

24. Participants with histologically confirmed advanced NSCLC previously treated with approved PD-L1/PD-1 inhibitors and platinum based chemotherapy, either sequentially or concurrently.
    - Eligibility of participants receiving previous treatment with non-approved anti PD-1 or anti-PD-L1 inhibitors or combination treatment with other non-approved agent(s) *may be discussed with* the Medical Monitor prior to enrollment. *The decision to enroll the patient in the study is the responsibility of the Investigator.*
25. Patients must be PD-L1 (+) defined as ≥ 1% PD-L1 expression based on immunohistochemistry using antibody clone 22c3, sp263 or 28-8. Expression will be determined in a fresh tumor biopsy collected during study screening or a possibly available archival sample, provided that the latter is not older than 12 months and has been obtained after failure of last CPI treatment line and prior to receiving study treatment.
26. Participants must have experienced Investigator assessed initial clinical benefit (stable disease or better) from most recent CPI therapy for at least 4 months.
    - If a scan within the first 4 months exists and shows progressive disease the patient is not eligible, (i.e. the scan result cannot be overruled by Investigator assessment of clinical benefit).
    - Should a subsequent scan for the same line of treatment show clinical benefit after initial radiographic progression (i.e. pseudoprogression) the patient is eligible.
27. Patients should have had only one CPI and one platinum based regimen, whether sequentially or concurrently. The acceptable sequences are:
    - Platinum-based chemotherapy (1L) + CPI treatment (1L); i.e., study treatment is second line therapy
    - Platinum-based chemotherapy (1L) → CPI treatment (2L); i.e., study treatment is third line therapy
    - CPI treatment (1L) → Platinum-based chemotherapy (2L); i.e., study treatment is third line therapy
        - Adjuvant chemo-radiation treatment with anti-PD-1/PD-L1 inhibitors or consolidation treatment with anti-PD-1/PD-L1 inhibitors after definitive chemo-radiation therapy is allowed but participants do require an additional line of anti-PD-1/PD-L1 treatment in the metastatic setting.

Specific Inclusion Criteria for Part B3 Expansion in PD L1 High, CPI Naïve, First Line NSCLC Cohort

28. Participants with histologically confirmed advanced NSCLC with PD-L1 high defined as ≥ 50% PD-L1 expression based on immunohistochemistry using antibody clone 22c3, sp263, or 28-8. Expression will be determined in a fresh tumor biopsy collected during study screening or a possibly available archival sample, provided that the latter is not older than 12 months and has been obtained after failure of last CPI treatment line and prior to receiving study treatment.

Specific Inclusion Criteria for Part B4 Expansion in CPI-Naïve SCLC Cohort

29. Participants must have histologically confirmed SCLC.
30. Participants may have had prior chemotherapy, radiation therapy or declined approved therapies for SCLC.

Additional Specific Inclusion Criteria for Part B5: CPI Naïve Esophageal Squamous Cell Carcinoma

31. Participants whose major lesion was histologically confirmed squamous cell carcinoma or adenosquamous cell carcinoma of the esophagus.
32. Patients who have previously received not more than 1 prior lines of treatment for metastatic disease prior to enrolling to the study. The prior line must be a fluoropyrimidine and platinum-based regimen and patients must have experienced progressive disease.
33. Patients who underwent a radical resection (R0 resection confirmed) in conjunction with chemotherapy with fluoropyrimidine and platinum-based drugs including neo-adjuvant/adjuvant therapy and chemo-radiation (including patients who underwent chemo-radiation followed by salvage surgery) are allowed.
    - If recurrence was confirmed by imaging within 24 weeks after the last dose of the treatment, the therapy should be counted as equivalent to metastatic treatment. Such patients are eligible and do not require an additional line of therapy in the metastatic setting.
    - If recurrence occurred later than 24 weeks after the completion of the initial neo-adjuvant/adjuvant therapy the patients need to be exposed to an additional line of fluoropyrimidine and platinum-based drugs in the metastatic setting to be eligible for the study - unless the investigator considers the patient not eligible for the re-exposure with fluoropyrimidine and platinum-based drugs.

5.2 EXCLUSION CRITERIA

General Exclusion Criteria for Parts A and B

Participants are excluded from the study if any of the following criteria apply prior to dosing on Cycle 1, Day 1:

1. Pregnancy, lactation, or breastfeeding.

2. Known hypersensitivity to any of the components of RO7121661, including but not limited to hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

Medical Conditions

3. Known symptomatic central nervous system (CNS) metastases.
    - Participants with previously treated brain metastases may participate provided they:
    - Are stable (without evidence of progression by CT or MRI for at least 4 weeks prior to Cycle 1/Day 1).
    - Have no evidence of new or enlarging brain metastases within at least 4 weeks from Cycle 1/Day 1.
    - Are off systemic steroids for at least 28 days prior to Cycle 1/Day 1
4. Spinal cord compression not definitively treated with surgery and/or radiation or without evidence that disease has been clinically stable for $\geq$ 2 weeks before Cycle 1/ Day 1.
5. Active or history of carcinomatous meningitis/leptomeningeal disease. Known asymptomatic CNS primary tumors or metastases if they have requirement for steroids or enzyme-inducing anticonvulsants in the last 28 days prior to Cycle 1/ Day 1.
6. Participants with an active second malignancy. Concurrent malignancy exceptions include: curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer and any previously treated early stage non-hematological malignancy that has been in remission for at least two years.
7. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders, and known autoimmune diseases or immune deficiency, or other disease with ongoing fibrosis (such as scleroderma, pulmonary fibrosis, emphysema, neurofibromatosis, palmar/plantar fibromatosis, etc.).
8. Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
9. Severe dyspnea or requiring supplemental oxygen therapy at rest.
10. Significant cardiovascular/cerebrovascular vascular disease within 6 months prior to Day 1 of study drug administration, including any of the following:
    - hypertensive crisis/encephalopathy
    - unstable angina
    - transient ischemic attack/stroke
    - congestive heart failure (for NYHA classification, refer to inclusion criteria)

- serious cardiac arrhythmia requiring treatment (exceptions are atrial fibrillation, paroxysmal supraventricular tachycardia)
- history of thromboembolic events (such as myocardial infarction, stroke or pulmonary embolism)

11. Known active or uncontrolled bacterial, viral, fungal, mycobacterial (including but not limited to tuberculosis [TB] and typical mycobacterial disease), parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 4 weeks prior to the start of drug administration.
12. Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease.
13. Major surgical procedure or significant traumatic injury (excluding biopsies) within 28 days prior to Cycle 1, Day 1 (i.e., first RO7121661 infusion), or anticipation of the need for major surgery during the course of the study.
14. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the participant at high risk from treatment complications.
15. Dementia or altered mental status that would prohibit informed consent.
16. Uncontrolled pleural effusion (with the exception of participants with indwelling catheters, e.g. PleurX®), pericardial effusion, or ascites requiring recurrent drainage procedures (expected to occur once monthly or more frequently).
17. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
    - Participants with a history of autoimmune-mediated hypothyroidism or endocrinopathy who are on thyroid-replacement hormone or appropriate replacement therapy are eligible for the study.
    - Participants with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Participants with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        - Rash must cover $<10\%$ of body surface area
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids

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

Prior/Concomitant Therapy

18. Vaccination with live vaccines within 28 days prior to the start of treatment.
19. For Part A, Part B1 (CPI experienced melanoma patients) and Part B2 (CPI and platinum experienced NSCLC patients), prior treatment with CPIs, immunomodulatory mAbs, and/or mAb derived therapies is allowed, with the following exceptions:
    - $<$ 4 weeks have elapsed between the last dose of prior anti-PD-1 and the proposed Cycle 1, Day 1
    - $<$ 5 half-lives or 28 days (whichever is shorter) have elapsed from prior treatment with specific immunomodulators, TLR agonists, inhibitors of IDO/TDO, or agonists (e.g., OX40)
    - Prior treatment with adoptive cell therapies, such as CAR-T therapies is not permitted
20. Prior treatment with a TIM-3 inhibitor is prohibited.
21. Concurrent therapy with any other investigational drug (defined as treatment for which there is currently no regulatory authority-approved indication) $<$28 days or 5 half-lives of the drug, whichever is shorter, prior to the first RO7121661 administration on Cycle 1, Day 1 is prohibited.
22. Immuno-modulating agents:
    - Last dose with any of the following agents, for example, etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, or efalizumab (or similar agents)$<$28 days prior to Cycle 1, Day 1 is prohibited.
    - Regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease) is prohibited.
23. Chronic use of steroids (excluding topical and inhaled) and concurrent high doses of systemic corticosteroids will not be allowed. Participants receiving baseline corticosteroid therapy ($>$ 10 mg prednisone/day or equivalent) within 1 week prior to the first dose of study drug are excluded.
24. Radiotherapy within the last 4 weeks before start of study drug treatment is not allowed, with the exception of limited palliative radiotherapy.
25. *Enrollment of participants who require blood transfusion (before and after the start of the study) is at the discretion of the Investigator. The Medical Monitor/Sponsor is available to the Investigator to advise and answer any question as needed.*

Specific Exclusion Criteria for Part B1 and Part B2 Expansion cohorts (CPI experienced patients)

26. Any history of an immune-mediated Grade 4 adverse event attributed to prior cancer immunotherapy (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase)
27. Any history of an immune-mediated adverse event attributed to prior CIT (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase) that resulted in permanent discontinuation of the prior immunotherapeutic agent.
28. All immune-mediated adverse events related to prior immunomodulatory therapy (other than endocrinopathy managed with replacement therapy or stable vitiligo) must have resolved completely to baseline. Participants treated with corticosteroids for immune-mediated adverse events except for corticosteroids replacement therapy for adrenal insufficiency (provided that the patient receives $\leq$ 10 mg prednisone/day or equivalent), must demonstrate absence of related symptoms or signs for $\geq$ 4 weeks following discontinuation of corticosteroids.

Specific Exclusion Criteria for Part B3 Expansion (1st line CIT naïve patients)

29. Prior therapy for metastatic disease is not permitted i.e., treatment with any immune CPIs (such as anti-PD-L1/PD-1, CTLA-4), immunomodulatory mAbs, other immunomodulator therapies, chemotherapy or TKIs.
30. Adjuvant anti-PD-1 or anti-PD-L1 therapy is not allowed. Adjuvant chemotherapy is permitted as long as treatment was administered $>$6 months prior to Cycle 1, Day 1.

Specific Exclusion Criteria for NSCLC patients (Part B2)

31. NSCLC patients with the following mutations, rearrangements, translocations are not eligible for Part B2: EGFR; ALK; ROS1, BRAFV600E, NTRK

Specific Exclusion Criteria for Part B4 Expansion (CPI-naïve SCLC patients)

32. Prior therapy with any immune CPIs (such as anti-PD-L1/PD-1, anti-CTLA-4), is not permitted.

Specific Exclusion Criteria for Part B5: CPI Naïve Esophageal Squamous Cell Carcinoma

33. Prior therapy with any immunomodulatory agents including CPIs (such as anti-PD-L1/PD-1, anti-CTLA-4), is not permitted.

5.3 LIFESTYLE CONSIDERATIONS

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

5.4 SCREEN FAILURES

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

All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before entering 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, *after advice from the Sponsor*. In case of uncertain or questionable results, any of the tests performed during Screening may be repeated before study drug administration to confirm eligibility (or clinical significance).

Biopsy samples will only be entered in the eCRF and analyzed for enrolled participants.

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 using pre-screening enrollment logs, Institutional Review Board (IRB)/Ethics Committee (EC) approved newspaper/radio advertisements, and mailings 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.

All investigational medicinal products (IMPs) required for completion of this study (RO7121661) will be provided by the Sponsor. All study drug administration will be at the study center under supervision of site staff.

6.1 TREATMENTS ADMINISTERED

Table 5 summarizes the treatments administered.

Table 5 Summary of Treatments Administered

	Ro 712-1661/F01-01 (Active)	Ro 712-1661/F02-01 (Diluent)
Administration	Intravenous [a]	
Dosage form	Concentrate for solution for i.v. infusion	Solution for infusion. For i.v. infusion
Concentration of RO7121661	50 mg/mL	0 mg/mL
Primary packaging	6-mL colorless glass vial	20-mL colorless glass vial
Extractable volume	6.0 mL	20.0 mL

[a] 0.2-μm inline filter to be used for drug administration.

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

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

6.1.1 RO7121661

Ro 712-1661/F01-01 drug product can be administered IV, either undiluted or diluted, as directed in the study protocol and the Pharmacy Manual. If diluted, Ro 712-1661/F01-01 drug product must be diluted either in 0.9% (w/v) sodium chloride solution or in the Sponsor's diluent, Ro 712-1661/F02-01, as directed in the Pharmacy Manual. A 0.2 μm inline filter must be mandatorily used with the infusion set during administration.

In Part A, the initial dose and subsequent infusions of RO7121661 will be delivered over 120 ± 10 minutes (although the infusion may be slowed or interrupted for participants

who experience infusion-associated symptoms; see Section 8.3.8.1), followed by a 90-minute observation period. If no IRR has been reported, the catheter may be removed at the end of the observation period.

In Part B, the initial dose of RO7121661 will be delivered over 120 ± 10 minutes (although the infusion may be slowed or interrupted for participants who experience infusion-associated symptoms; see Section 8.3.8.1), followed by a 90-minute observation period. If the 120-minute infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 60 ± 10 minutes, followed by a 60 minute observation period. If the 60-minute infusion is well-tolerated, all subsequent infusions may be delivered over 30 ± 10 minutes, followed by a 30-minute observation period. If no IRR has been reported, the catheter may be removed at the end of the observation period.

During infusion, vital signs (including, if possible, supine diastolic and systolic blood pressure, pulse rate, and temperature) must be monitored as described in the SoA (Section 1.3). Vital signs during the infusion are not required to be captured in the eCRF, unless abnormalities are observed.

If feasible, the line for drawing blood for PK samples (opposite extremity to the one with the infusion line) will remain in place until the 24-hour sample is taken.

Dose, date, and time of the infusion start, date and time of end of infusion, total dose administered, interruption or adjustment of infusion rate, and reason will be recorded for each participant. If the infusion is interrupted, the date and time of stopping and resuming will be recorded.

6.1.2 Pre-medication

No pre-medication is foreseen prior to the first administration of RO7121661.

However, if administered, all pre-medications should be captured as concomitant medications in the participant's electronic Case Report Form (eCRF).

If Grade ≥ 2 IRRs or tumor inflammatory events occur in the majority of participants during dose escalation, the utility of prophylactic pre-medications including paracetamol and antihistamine may be considered for newly enrolled participants and premedication regimen and schedule should be *discussed* between Sponsor and Investigator(s).

Participants who experienced a Grade 2 or higher IRR on a previous infusion should be pre-medicated for subsequent infusions. 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 H1/2 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 RO7121661 administrations. The event will be reported as a single AE (e.g., fever). Pre-medication with corticosteroids for those participants at subsequent infusions needs approval from the Sponsor and the treatment and management at the time of a single and isolated event is at the discretion of the Investigator.

All pre-medications should be captured as concomitant medications in the participant's electronic Case Report Form (eCRF).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

The packaging and labeling of the study medication will be in accordance with Roche 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 utilizing the Pharmacy Manual.

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in

accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

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

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

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

Study NP40435 is a non-randomized open-label study. The specific treatment to be administered to the participant will be assigned using an IRT. An IRT User Guide will be provided to each site.

6.4 TREATMENT COMPLIANCE

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

6.5 CONCOMITANT THERAPY

For the purpose of the study, RO7121661 is considered investigational medicinal product (IMP). All other medications given during the study are considered non-IMPs.

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 *can advise* if there are any questions regarding concomitant or prior therapy.

All concomitant medications *or vaccines* should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). All therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

Radiotherapy

Participants should not receive study treatment during radiation treatment.

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

- Days where RO7121661 is administered.
- During the DLT evaluation window.
  - If radiotherapy is administered during the DLT evaluation window, the participant will not be evaluable.

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 and therapy for pre-existing conditions, unless the rationale for exception is discussed and clearly documented.

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

- Investigational or unlicensed/unapproved agents
- Immunotherapy/radio-immunotherapy
- Chemotherapy / targeted therapy
- Radiotherapy (with the exception of limited field palliative radiotherapy).
- Biologic agents (e.g., bevacizumab, cetuximab).
- Chronic use of steroids (inhaled and topical steroids are permitted) at baseline of $>$10 mg of prednisone/day or equivalent. Concurrent high doses of systemic corticosteroids will not be allowed.
- 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

Instructions for RO7121661 administration, change of infusion rate, and interruption of infusion are provided in Section 6.1 and Section 7.

Participants who experience toxicities fulfilling the definition of a DLT in the first cycle, or DLT-equivalent toxicities in subsequent cycles should be discontinued from study treatment. Nevertheless, the Investigators, after discussion with the Sponsor, will have the option to reduce the dose of RO7121661 to the previous tolerated dose level, if participant is deemed to be deriving clinical benefit.

A delay of RO7121661 administration for up to two cycles, will be acceptable to allow for resolution of toxicity to NCI CTCAE Grade ≤ 2 for hematological toxicities or Grade ≤ 1 for non-hematological toxicities (with the exception of a toxicity considered as non-RO7121661 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 RO7121661 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 $discussed$ 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.

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

Investigators are encouraged to contact the Sponsor for further guidance if needed. After Cycle 1 is completed, dose modifications should be discussed with the Sponsor. In these instances, a confirmation with the Sponsor is requested and documentation in the eCRF is requested. Treatment delays of up to 3 days due to logistical considerations (e.g., center closure for holiday) are generally acceptable and do not need to be discussed with the Sponsor. In no instance are cycles shorter than 14 days of duration (i.e. Q2W) allowed in this study.

For participants on treatment for at least 4 cycles, minor elective surgery will be permitted with resumption of treatment as soon as possible post-procedure, assuming normal recovery (see Section 7.1.1 for temporary interruption or dose delay). This can

be done to allow participants who could potentially benefit from RO7121661 to remain on the study treatment.

6.7 TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide RO7121661 or any other study treatments or interventions to the participants after the end of the study or when participants discontinue or have been withdrawn from the study. The Sponsor will evaluate whether to continue providing RO7121661 to participants after the main study is over, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

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

7.1 DISCONTINUATION OF STUDY TREATMENT

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.

Participants must permanently discontinue study treatment if they experience any of the following (also see Appendix 6):

- Intolerable toxicity related to study treatment, including development of an immune mediated adverse event determined by the Investigator to be unacceptable given the individual participant's potential response to therapy and severity of the event
- Pregnancy.
- Grade 4 IRR.
- IgE-mediated hypersensitivity reactions, including anaphylaxis.
- Any toxicity which is not manageable with dose delays (as allowed per protocol), dose decrease, and appropriate treatment.
- Unacceptable toxicity as determined by Investigator.

- For cardiac changes:
    - If a clinically significant finding is identified (including, but not limited to QTcF ≥ 500 ms and/or an increase of ≥ 60 ms in QTcF from screening), the Investigator or qualified designee will determine if the participant can continue in the study and if any change in clinical management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the participant.
- Participant non-compliance, specifically defined as disregarding protocol.
- Symptomatic disease progression when there is a consensus that the participant will not benefit from study treatment.

As with other immunotherapies, treatment beyond RECIST Version 1.1 progression may be considered following discussion between the Investigator and the Sponsor. When considering treatment beyond progression, locally approved and available treatment options need to be taken into account.

The criteria below are needed for continuing treatment beyond initial apparent progressive disease per RECIST Version 1.1 (e.g., radiological progression secondary to tumor inflammation):

- Absence of clinically important symptoms and signs (including worsening of laboratory values) indicative of disease progression
- Investigator-assessed potential clinical benefit for the participant
- The participant is tolerating study drugs.
- No decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Participants who discontinue study treatment 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 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 **and will not be entered into the database**.

- Participants who fail to complete their DLT assessment period because of non-drug-related reasons.

- In the case of a major protocol violation participants will be excluded from the MTD/DLT analysis but might continue the treatment if deemed beneficial, and if there is no safety concern associated with the protocol violation criteria and according to clinical judgment.

Participants will be treated until disease progression, loss of clinical benefit, unacceptable toxicities, or withdrawal from treatment for other reasons, or death.

7.1.1 Temporary Interruption

Before permanently discontinuing study treatment (regardless of whether initiated by the participant, the Investigator or Sponsor), an interruption should be considered. Participants, who have temporarily interrupted study treatment, should be considered to re start as soon as medically justified in the opinion of the Investigator.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will depend on the $discussion$ between the Investigator and the Medical Monitor.

In case of toxicity requiring RO7121661 treatment to be put on hold, the study treatment should only re-start once the toxicities have resolved to NCI CTCAE Grade ≤ 2 for hematological toxicities or Grade ≤ 1 for non-hematological toxicities. Participants who do not recover from drug-related toxicities after omission of up to 2 doses (delay of 4 weeks in the Q2W schedule) of RO7121661 and who in the opinion of the Investigator are not receiving clinical benefit from RO7121661 treatment, should be permanently discontinued from the study.

If in the judgment of the Investigator, the participant is likely to derive clinical benefit from RO7121661 after a hold of more than 2 doses, study drug may be re-started.

If an IRR develops, the infusion of RO7121161 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). Study treatment should be re-started as soon as medically justified in the opinion of the Investigator.

7.1.2 Resumption of Study Treatment

If a participant has a complete response (CR) or achieves maximum clinical benefit as determined by the Investigator and the Sponsor after an integrated assessment of radiographic data, biopsy results (if available), and clinical status, the study treatment

may be paused at the discretion of the treating physician after *discussion* with the Medical Monitor. The participant may remain on study and be followed according to the SoA (Section 1.3). If the disease relapses or progresses, the study treatment may be resumed after consultation with the Medical Monitor.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines, may jeopardize the participant's safety if he/she continues in the study. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he/she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the participant.
- Participant non-compliance.

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 will be replaced (see Section 7.1).

See 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.

7.3 LOST TO FOLLOW-UP

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time-points are summarized in the Schedules of Activities (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.

Certain samples for exploratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Based on continuous analysis of the data in this study, any sample type or time-point 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 response will be evaluated according to RECIST Version 1.1 (see Appendix 7) and modified criteria for immunotherapies (see Appendix 8 for iRECIST). Response will be assessed by the Investigator on the basis of physical examinations and CT scans (or magnetic resonance imaging [MRI]) of chest, abdomen, and pelvis as defined in the SoA (Section 1.3). CT scans of the neck should be included, if clinically indicated. Ultrasound and X rays are not acceptable for monitoring target lesions. All measurable disease must

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

In case of clinically measurable superficial (such as skin) lesions, repeated photographs should be used to document tumor response (Section 8.1.2).

The data collected for RECIST v1.1 will be used by the Sponsor to calculate programmatically timepoint responses for iRECIST, a recently published guideline developed by the RECIST working group in an effort to harmonize immune-based response criteria across the academic and industrial cancer immunotherapy field (Appendix 8).

In the absence of clinical deterioration, any initial assessment of radiological progressive disease or mixed response should be confirmed by a repeat evaluation at the next time point for tumor assessment. As with other immunotherapies, treatment beyond RECIST progression could be considered after approval of the Sponsor. The criteria needed for continuing treatment beyond initial apparent progressive disease (e.g., radiological progression secondary to tumor inflammation) are described in Section 7.1.2.

Tumor assessment will be performed at the time points described in the SoA (Section 1.3). All tumor assessments after baseline may be done within $\pm$7 days of the scheduled visit. Confirmation of objective responses (partial and complete responses) will be done at the next scheduled visit after at least 28 days from the initial response. If disease progression is determined solely by symptomatic deterioration, a RECIST Tumor Assessment eForms must be completed at that time indicating disease progression. At the Investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

8.1.2 Photography of Cutaneous Lesions

Cutaneous lesions not evaluable by CT or MRI will be documented by color digital photography, including a ruler to estimate lesion size. Cutaneous lesions may be considered target lesions if they meet RECIST 1.1 criteria (see Appendix 7), otherwise they may be considered non-target lesions.

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

8.2 SAFETY ASSESSMENTS

Planned time-points for all safety assessments are provided in the SoA (Section 1.3). On dosing days, the safety assessments are to be performed prior to the study treatment administration. If the assessments have been performed within maximum 72 hours prior to dosing, they do not need to be repeated on the scheduled dosing day.

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck and lymph nodes systems. Height and weight will also be measured and recorded. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen)
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

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 adverse events on the Adverse Event eCRF.

8.2.2 Royal Marsden Hospital Risk Score

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

8.2.3 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status will be assessed as specified in the SoA (Section 1.3). It is recommended, where possible, that a participant's Performance Status will be assessed by the same person throughout the study.

8.2.4 Vital Signs

Routine vital signs including supine diastolic and systolic blood pressure, pulse rate, respiratory rate, and body temperature will be assessed as specified in the SoA (see Section 1.3), including during infusions of RO7121661. Vital signs during the infusion are not required to be captured in the eCRF, unless abnormalities are observed.

Blood pressure and pulse measurements will be assessed 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).

Participants experiencing Grade ≥ 3 vital sign abnormalities on the day of any administration of study treatment or at a previous cycle should stay at site for the next study treatment administration for at least 24 hours post infusion. In case of drop in blood pressure associated with hemodynamic instability and/or abnormal HR, particularly arrhythmia, RO7121661 administration should be interrupted and the participant should be fully monitored until normal cardiac function is regained.

8.2.5 Electrocardiograms

Triplicate 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. Refer to Section 7.1 for QTc withdrawal criteria and additional QTc readings that may be necessary.

At each time-point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than approximately 2 minutes apart. The average of the 3 readings will be used to determine ECG intervals (e.g., PR, QRS, and QT). Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur. ECGs for each participant should be obtained from the same machine whenever possible.

To minimize variability, it is important that participants be in a resting position for at least 10 minutes prior to each ECG evaluation. 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 Roche, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction, see Appendix 9), QTcF (Fridericia's correction, see Appendix 9) and RR will be calculated by the Sponsor and

recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

8.2.6 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 CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- 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.

  If laboratory values from non-protocol specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) then, the results must be recorded in the AE CRF.

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

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

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

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.

8.2.7 Medical History and Demographic Data

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

Demographic data will include age, sex, and self‑reported race/ethnicity. Data on race and ethnicity will be used to explore associations between base-line demographic data and risk of adverse events.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 2. The non-serious adverse events of special interest 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 adverse events (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording adverse events 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 adverse events at each participant's contact. All adverse events, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

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

After initiation of study treatment, all adverse events, regardless of relationship to study treatment, will be reported until the last follow-up visit 60 days (Part A) and 90 days (Part B) after last dose. DLTs will be reported during the DLT assessment window.

Post-study adverse events and serious adverse events: The Investigator is not required to actively monitor participants for adverse events after the end of the adverse event reporting period – that is, after the last follow-up visit.

However, if the Investigator learns of any SAE (including a death) or other adverse events 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 adverse event 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 adverse event 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 serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

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

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

8.3.3.2 Sponsor Follow-Up

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

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

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

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

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

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical monitors is available 24 hours a day 7 days a week. 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 4 months after the final dose of RO7121661.

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 4 months after the final dose of RO7121661.

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

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

8.3.6 Non-Serious Adverse Events of Special Interest

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

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

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

No disease-related events have been identified for this study.

8.3.8 Management of RO7121661 Specific Adverse Events

Based on the MoA, PD-1/TIM-3 is expected to show a safety profile that is similar to other CPIs. Toxicities from CPIs can be divided into infusion reactions and immune-mediated adverse events (imAEs). Toxicities associated or possibly associated with RO7121661 treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology.

Measures will be taken to ensure the safety of participants participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of participants during the study. Administration of RO7121661 will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

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

8.3.8.1 Infusion-Related Reactions

Administration of therapeutic antibodies may cause IRRs characterized by symptoms such as fever, chills, dizziness, hypertension, hypotension, dyspnea, restlessness, sweating, flushing, skin rash, tachycardia, tachypnea, headache, tumor pain, nausea, and/or vomiting. Respiratory and cardiac symptoms such as, bronchospasm, larynx, and throat irritation, wheezing, laryngeal edema and atrial fibrillation may also occur. Such reactions typically occur during or shortly after an infusion or within 24 hours after study treatment infusion, predominantly at the first infusion. The incidence and severity typically decrease with subsequent infusions.

Participants may also develop immunoglobulin (Ig)E mediated hypersensitivity reactions. IRRs may be indistinguishable from an anaphylactic reaction; however, in case of IgE mediated hypersensitivity, symptoms typically occur after previous exposure and very rarely with the first infusion. In case of confirmed IgE mediated hypersensitivity reaction, treatment should be permanently discontinued.

No premedication is indicated for the administration of Cycle 1 of RO7121661. However, patients who experience a grade 2 or higher infusion-related reaction (IRR) with RO7121661 should receive premedication for subsequent infusions (see Section 6.1.2). In case of Grade 4 IRR related to RO7121661, the participant should be permanently discontinued from the study treatment. If an IRR occurs during the infusion of RO7121661, please refer to Table 6.

Table 6 Recommendations for RO7121661 Infusion-Related Reaction Prevention and Management

[a]Infusion-Related Reactions	Guidance
Grade 1−2	Slow infusion to ≤ 50% or interrupt infusion Give supportive treatment[b] Upon symptom resolution may resume infusion (if interrupted) at 50% starting rate. The infusion must remain at the lower rate resulting in symptom resolution for the remainder of the infusion. For grade 2 IRRs, subsequent cycles of RO7121661 should be administered with pre-medication including acetaminophen/paracetamol and an antihistamine, such as diphenhydramine. Notes: 1. For Grade 2 wheezing or urticaria, patient must also be pre-medicated prior to subsequent doses (as described above). 2. If symptoms recur with the same or greater severity following the slower or interrupted infusion, the infusion must be stopped immediately. No further RO7121661 will be administered for the cycle.
Grade 3	Discontinue infusion. No further RO7121661 will be administered for the cycle. Give supportive treatment[b] Subsequent cycles of RO7121661 should be administered with pre-medication including paracetamol, antihistamine and corticosteroids. [c] Notes: 1. If symptoms recur despite pre-medications with the same or greater severity at subsequent cycles, the infusion must be stopped immediately and patient permanently discontinued from study treatment. 2. Patients who experience Grade 3 wheezing, bronchospasm or generalized urticaria at first occurrence must be discontinued from study treatment.
Grade 4	Discontinue infusion immediately Give supportive treatment Permanently discontinue study treatment

[a] Refer to the NCI-CTCAE, v5.0 scale for the grading of symptoms.

[b] Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine, such as diphenhydramine, if they have not been administered in the last 4 hours. Intravenous fluids (e.g., normal saline) may be administered as clinically indicated. For bronchospasm, urticaria, or dyspnea, antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice.

[c] Subsequent infusions may be started at the original rate in consultation with the Medical Monitor.

8.3.8.2 Immune-mediated adverse events

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

Discontinuation of RO7121661 may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors. RO7121661 therapy may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of RO7121661 and the initiation of high-dose corticosteroids (prednisone, 1-2 mg/kg/day, or methylprednisolone, 1-2 mg/kg/day). Corticosteroids should be tapered over the course of at least 4-6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy. In general, permanent discontinuation of RO7121661 is recommended with grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement. The management guidelines for imAEs associated with RO7121661 are provided in Appendix 6.

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 adverse event 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/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:

- Contact the Sponsor's Medical Monitor immediately.

- Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
- Obtain a blood sample for PK analysis within 14 days from the date of the last dose of study treatment, if *advised* by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.

For this study, any dose of RO7121661 greater than 150% of the recommended dose level will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate concentrations of study treatment will be collected from an IV line from the arm opposite to that used for study treatment administration. The date and time of each sample collection will be recorded in the eCRF. RO7121661 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 RO7121661 can be adequately characterized (but without increasing overall blood collection volume for PK). This will be documented in a Note to File and a new SOA will be provided. Additional PK samples will be taken at the time of treatment discontinuation, if the participant experiences an infusion-related AE (such as an IRR), or if the participant experiences an AE leading to dose-reduction or delay of RO7121661 administration (see Section 6.6).

Remaining volumes of PK samples may also be used for additional PK/ADA analysis or assay development or validation, for RO7121661-related exploratory analyses, or to help develop further blood tests for exploratory analysis (e.g., further characterization of immune responses), after they are used for the mentioned intended use and as deemed appropriate.

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

8.5.1 Immunogenicity Assessments

Although RO7121661 is a human antibody, there is a risk that anti-drug antibody (ADA) against RO7121661 could develop, potentially reducing its efficacy and/or potentially resulting in symptomatic hypersensitivity reaction, in particular immune-complex reactions.

Antibodies to RO7121661 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 ≥ 2 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 RO7121661 concentration.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against RO7121661.The date and time of each sample will be recorded in the eCRF. If required, ADA positive samples will be further characterized in an exploratory assay.

If required, remaining ADA samples may also be used for additional exploratory analyses (e.g., further characterization of immune responses) and/or PK/ADA assay development/validation experiments after the mentioned intended uses, as deemed appropriate.

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

Details on sampling procedures, sample storage and shipment are documented in the Sample Handling Manual.

8.6 PHARMACODYNAMICS/EXPLORATORY BIOMARKERS

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

These samples will be tested for protein, nucleic acid, or other tissue or blood derived biomarkers relating to the proposed mechanism of action of RO7121661. These include, but are not limited to, drug RO, cellular profile and activation status of immune cells in blood and tumor, cytokines and other soluble markers of inflammation. Analysis techniques may include, but are not limited to, flow cytometry, immunohistochemistry, gene expression, and gene sequencing. DNA and/or RNA will be extracted for exploratory research on genetic biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways, or immune-mediated markers, microsatellite instability (MSI) and tumor mutational burden), and to enable genomic analysis for exploratory research on genetic biomarkers.

The specimens will also be used for research purposes to identify biomarkers useful for predicting and monitoring response to RO7121661 treatment, identifying biomarkers useful for predicting and monitoring RO7121661 safety, assessing PD effects of RO7121661 treatment, and investigating mechanism of therapy resistance. This may include retrospective and longitudinal testing of bacterial or viral infection (including but

not limited to SARS-CoV-2) by serological methods. These analyses may inform any association of bacterial or viral infection and response to treatment.

Additional markers may be measured in case a strong scientific rationale for these analyses develops. Any remaining samples after the specified analyses may also be used for additional (assay) validation experiments. Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to RO7121661, disease process, pathways associated with disease state, and/or mechanism of action of the study treatment. Note that as science and research is evolving, the list of biomarkers that will be evaluated cannot be fully defined.

Based on continuous analysis of data any sample type, time point, and/ or analysis not considered to be critical for safety may be stopped at any time if the data does not support a strong scientific justification to continue. During the course of the study, sampling time-points may be modified on the basis of emerging data to ensure the PD of RO7121661 can be adequately characterized (but without increasing overall blood collection volume). This will be documented in a Note to File and a new SOA will be provided.

Archival tumor blocks will be returned, unless notified by the site that they do not want it back. Blood, tissue and other residual material (slides, extracts, on-study blocks, etc.) will be destroyed within 2 years after the final closure of the clinical database unless the participant gives specific consent for the remainder of the material to be stored for optional exploratory research (RBR).

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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.

8.6.1 Blood Samples

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

- Blood samples will be collected for measurement of RO during dose escalation.
- Blood samples will be collected for measurement of cytokines/chemokines (e.g., IL-2, IL-6, IL-8, and IFNγ) and immune activation markers such as sCD25
- Blood samples will be collected for measurement of soluble target (PD-1, TIM-3)
- Blood samples will be collected for the measurement of IgE/Tryptase

- Blood for whole genome sequencing (see Section 8.7.1). If this sample is missing on Cycle 1 Day 1, it should be collected at the next scheduled visit, where possible

The following additional samples for PD and biomarker research are required and will be collected from Part B participants only

- Blood samples will be collected for flow cytometry. The samples will be analyzed for changes in the numbers and activation status of lymphocyte subsets including but not limited to CD4+, CD8+, and/ or NK cells
- Blood for RNA extraction will be collected for gene expression analysis
- Blood for bTMB
- Blood for ctDNA

8.6.2 Tissue Samples

8.6.2.1 Archival Tumor Samples

FFPE archival tumor tissue is to be obtained from all participants, if available. The primary and the most recent metastasis (if both are available) should be submitted for analysis. Ideally these samples should include the invasive margin. Tumor blocks are preferred but slides will be accepted. Samples will be collected for IHC and immunofluoresence analyses (such as, but not limited to, CD8/Ki67, PD-1, TIM-3, PD-L1). Samples may also be used for TMB or gene expression.

Archival tumor blocks will be returned to the sites when requested by the investigator or at the end of the study, unless notified by the site that they do not want it back.

8.6.2.2 Fresh Tumor Biopsies

Screening and on treatment fresh tumor biopsies may be required for additional participants (i.e., if dose cohort extended to confirm safety, PK and/or RO and/or the biomarker profile) in Part A1 and A2, unless otherwise specified by the Sponsor. In Part B, screening and on treatment biopsies are mandatory in all cohorts. In order to mitigate the potential risk associated with tumor biopsies, all participants required to have a biopsy must have tumor lesions from which biopsies can be safely obtained, as per clinical judgment of the treating physician.

The screening sample should be collected after eligibility is confirmed unless the fresh biopsy sample is needed to confirm patient eligibility (e.g. to confirm PD-L1 expression levels for Cohorts B2 and B3). Post dose samples can be collected $+2/-1$ day from scheduled time-point. If the participant progresses and discontinues treatment prior to on treatment biopsy day, the tumor biopsy should be taken at the time of treatment discontinuation. An additional biopsy at the time of partial response, stable disease, progression or at any other time-point of interest based on participants' course of disease may be taken after discussion between the Investigator and the Sponsor.

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

Collection of tumor biopsies should be guided by ultrasound, CT scan, or other methods according to the location of the selected lesion using a 16-gauge needle (preferred) to provide cores, ideally, of at least 20 mm in length or equivalent size. Ideally 4 (minimum 2) core biopsies will be obtained at each time-point (at the physician's discretion). Fine-needle aspiration is not acceptable. The biopsies will be taken from accessible tumor locations, including, but not limited to, skin, lymph node, rectum, liver etc. Bone biopsies and trans-bronchial biopsies are not acceptable.

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

Additional participants may be enrolled in Part B in the event that paired fresh baseline and on-treatment biopsies are not evaluable for the key biomarker analyses to ensure that at least 60% of paired fresh biopsy samples are evaluable to conclude the PD analysis.

In the event that a fresh biopsy is taken during the screening period and the participant is not enrolled into the study, the fixed and embedded biopsy (FFPE block) can be returned to the site upon site request. The site must confirm that a written consent is obtained from the participant before return request submission to Roche. If the participant does enroll in the study, fresh biopsies will not be returned to the site.

Biopsies will be used for IHC (e.g., CD8/Ki67, PD-1, TIM-3, PD-L1), TMB and gene expression.

8.7 GENETICS

8.7.1 Whole Genome/Exome/Targeted DNA Analysis

At participating sites, blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) to identify mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. The DNA may also be used to determine if alleles at genes associated with immunity, such

as KIR and HLA alleles, affect the PK/PD/efficacy/safety of the treatment. Research may distinguish germline mutations from somatic mutations. The samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol will not be applicable at that site.

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 or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events. 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 and characterization of important biomarkers and pathways to support future drug development.

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

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

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

8.8 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.8.1 Overview of the Research Biosample Repository

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

Specimens will be collected from participants who give specific consent to participate in this optional Research Biosample Repository. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, 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.

8.8.2 Sample Collection

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Saliva for DNA extraction

Saliva will be collected to assess comparability of DNA extraction from saliva and whole blood. This collection will serve as a pilot for an overall strategy to decrease participant burden and blood volume collection for DNA extraction in exploratory research.

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7121661 or diseases:

- Leftover blood samples
- Leftover tissue samples

The samples collected for DNA extraction 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 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. Participant will not be identified by

name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, WGS 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 Research Biosample Repository storage period will be in accordance with the IRB/EC‑approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

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

8.9 HEALTH ECONOMICS

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. Informed Consent Forms (ICFs) for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments 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) unless indicated in the SoA (see Section 1.3).

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 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 schedule of assessments.

8.10.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the study or discontinue from the study early will be asked to return to the clinic 28 days (±7 days) after the last dose of study drug for a follow-up visit (see Section 1.3). The visit at which response assessment shows progressive disease may be used as the study completion/early termination visit.

8.10.4 Follow-Up Assessments

Participants will be treated with study treatment, until disease progression, unacceptable toxicity, or withdrawal of consent. Participants may continue study treatment for 24 months *or longer if the participant is still benefitting from treatment at the time of last visit at the end of the two-year period.*

As with other immunotherapies, treatment beyond RECIST progression could be considered after approval by the Sponsor. The criteria needed for continuing treatment beyond initial apparent progressive disease per RECIST Version 1.1 (e.g., radiological progression secondary to tumor inflammation, TLS) are outlined in Section 7.1.

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

8.10.4.1 Post-Study Safety Follow-up

The sites will provide to the Sponsor an update on safety status 60 days (±7 days) after last treatment for Part A and 90 days (±7 days) after last treatment for Part B.

8.10.4.2 Post-study Survival Follow-up

The sites will provide to the Sponsor an update on survival status 90 days (±7 days) after last treatment and then every 3 months thereafter up until 24 months *(48 months for the extended treatment period)* post initial treatment for each participant enrolled in the study. Contact can be either in person or via a phone call to document; the sites will use a designated section of the eCRF for this purpose.

8.10.5 Assessments at Unscheduled Visits

Please see Section 1.3 for activities that are required to be performed in case of an unscheduled visit. For an unscheduled visit in the event of an IRR or hypersensitivity

event ≥ Grade 2 or AE leading to dose reduction or delay, please see Section 8.3.8.1 and Appendix 6.

9. STATISTICAL CONSIDERATIONS

The data will be analyzed by the Sponsor and/or designated contract research organization. Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation.

When appropriate, data will be summarized by dose cohort and regimen within each part.

9.1 STATISTICAL HYPOTHESES

Not applicable

9.2 SAMPLE SIZE DETERMINATION

This study is intended to obtain preliminary safety, PK, PD, and activity information in the treated populations, and the sample sizes do not reflect explicit power and Type I error considerations.

The maximum planned enrollment for this study is approximately 270-280 participants for both Parts A and B.

For the dose escalation stage in Part A, up to [redacted] DLT evaluable participants are planned for the Q2W schedule with an additional [redacted] participants if confirmation of safety, PK, RO and/or biomarkers are needed prior to opening Part B cohorts. The exact sample size cannot be pre-determined and depends on the number of cohorts needed to reach the MTD/RDE with the maximum planned dose set at 2.1 g.

Up to approximately [redacted] participants may be enrolled in the expansion stages across the indication-specific cohorts in Part B.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 7.

Table 7 Analysis Populations

Population	Description
Dose Limiting Toxicity	The DLT-evaluable population is defined as all participants who received at least two doses of study medication and either: experienced a DLT within the DLT period OR cleared the DLT period without a DLT The DLT period is 21 (Q2W) from Day 1/Cycle 1 to Day 7/Cycle 2. If there is a delay in Cycle 2 treatment the DLT period should be adjusted to cover Day 7/Cycle 2 up to a maximum of 35 (Q2W) days, since the maximum dose delay allowed is 14 days.
Efficacy	All participants in the safety population who received at least one dose of study drug and who have at least one baseline and one on-study tumor assessment. Participants who received at least one dose of study drug and discontinued the study because of progression before the first on-study tumor assessment will be considered as response-evaluable.
Safety	All participants who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis. Unless otherwise specified, the safety population will be the default analysis set used for all analyses.
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.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Demography and baseline characteristics (including age, sex, participant disposition, previous therapies, and medical history) will be analyzed using descriptive statistics. The analysis will be based on the safety analysis population. Data will be summarized by dose cohort and regimen within each part.

9.4.2 Efficacy Analyses

The primary and secondary efficacy analyses listed in Table 8 will include all participants in the efficacy population with participants grouped according to dose cohort within each study part.

Table 8 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
According to RECIST Version 1.1 criteria and iRECIST: • Objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DoR) • Progression-free survival (PFS)	No formal statistical model and no formal hypothesis testing are planned in this study. Tumor response data will be reported using descriptive statistics. Response data will be listed. ORR and DCR will be summarized by using relative frequencies and 90% confidence interval (CI). If data are sufficient, duration of response and PFS will be summarized by using time-to-event analyses and Kaplan-Meier curves. The above analyses will be carried out for RECIST Version 1.1 (primary analysis) and iRECIST (exploratory analysis).
Overall Survival (OS)	OS data may be tabulated and summarized using time-to-event analyses and Kaplan-Meier curves if data is collected and mature. Eventually, summaries will be carried out by cohort separately for each part.

Objective response rate (ORR) and disease control rate (DCR) are determined as the rate of participants with an objective tumor response of CR or partial response (PR) (ORR) or CR, PR or stable disease [SD] (DCR). For this protocol, confirmation of response is required at least 4 weeks after a first response occurred. To classify a response as SD, measurements will have to be classified as stable (according to RECIST Version 1.1) at least once at a minimum of 4 weeks after study entry.

In the primary analysis ORR and DCR will be derived for RECIST Version 1.1 and will be based on Investigators' assessment. Participants with missing or no response assessments will be classified as not evaluable unless there is documented clinical deterioration, in which case participant will be classified as non-responders.

DoR will be calculated for participants who have a best (confirmed) overall response of CR or PR and will be defined as the time from first occurrence of a documented response until the time of documented disease progression or death (death within 30 days from last study treatment) from any cause, whichever occurs first. Censoring methods will be the same as the one applied for progression-free survival (PFS).

PFS will be defined as the time from study treatment initiation (Cycle 1 Day 1) to the first occurrence of documented disease progression (based on RECIST Version 1.1 Investigator's assessment) or death from any cause, whichever occurs first. For

participants who do not have documented progressive disease or death during the study, PFS will be censored at the day of the last tumor assessment.

Sensitivity analyses of response endpoints (ORR, DRC, DoR, and PFS) may include the evaluation of response according to iRECIST.

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

9.4.3 Safety Analyses

Unless otherwise specified all safety analyses listed in Table 9 will be based on the safety population. All safety parameters will be analyzed using descriptive statistics, summarized and presented in tables. Data will be summarized by dose and regimen (if applicable) within each part.

Safety will be assessed through summaries of DLTs (for Part A), adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study treatment.

Table 9 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
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, using the most up-to-date version of the MedDRA terminology for AEs and diseases. AEs will be graded according to NCI CTCAE grades v5.0. Adverse events will be summarized by mapped term and appropriate thesaurus level. Toxicity grade, seriousness, and relationship to study treatment will be presented, as well as summaries of deaths, AEs leading to death and premature withdrawal from study treatment. Glossary of AEs, medication, and procedures will be provided.
Nature and frequency of DLTs	DLT events will be presented by individual listings. The MTD will be estimated with a 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 (Standard International) 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, as appropriate.
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 dose level.

AE = adverse event; DLT = dose-limiting toxicity; ECG = electrocardiogram; eCRF = electronic cases report form; EWOC = Escalation with overdose control; mCRM = modified Continuous Reassessment Method; MedDRA = Medical Dictionary for Regulatory Activities; MTD = maximum tolerated dose; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

9.4.4 Pharmacokinetic Analyses

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 dose levels and/or dosing regimen.

Individual and mean serum RO7121661 concentration versus time data will be tabulated and plotted by dose levels and/or dosing regimen. Graphical displays of PK data may also be provided. The serum PK of RO7121661 will be summarized by estimating total exposure (AUC), maximum concentration, total clearance, volume of distribution at steady‑state, and terminal half-life (when applicable). Estimates for these parameters will be tabulated and summarized. Inter‑participant variability and drug accumulation will be evaluated.

9.4.5 Immunogenicity Analyses

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

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

- Participants are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment-enhanced ADA response).
- Participants are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment unaffected).

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

9.4.6 Pharmacodynamic Analyses

The PD analysis will be based on the availability of evaluable blood or tumor samples. PD parameters will be listed by participant. Parameters may be tabulated by dose-level/regimen and time-point. Depending on findings, descriptive statistics may be used in summarizing relevant peripheral blood and tumor PD markers. Absolute change from baseline may be calculated for the PD markers. Graphical techniques may be employed to better understand the relationship of the PD markers with dose and time. Correlations

between PD markers, PK of RO7121661, and clinical response may be assessed through data tabulations and graphical techniques. The potential prognostic value of the PD markers may also be investigated.

9.5 INTERIM ANALYSES

It is anticipated that at least one interim analysis will be conducted in Part B of the study, with the earliest interim analysis taking place when at least [redacted] participants have been enrolled per expansion, and participants have been followed for a minimum of 18 weeks. If no complete or partial responses are observed, enrollment will be stopped.

In general, predictive probabilities might be used to guide eventual additional interim analyses of clinical activity compared with expected activity from the SoC.

These futility analyses are not binding and may be overruled if other endpoints (such as DCR rate, DoR, PFS, or OS) show significant improvement over the expected benefit in the population.

Recruitment will not be interrupted while waiting for data maturity.

At any time during the study, parts, cohorts, and arms may be closed based on emerging data external to the study or operational reasons.

9.6 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

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

The Investigator should follow the requirements for reporting all 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/EC, and archived in the site's study file.

1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable,

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

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

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

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

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

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

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

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will

be told that they are free to refuse to participate and may withdraw their 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/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site

Withdrawal from the Research Biosample Repository

Participants who give consent to provide 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 NP40435 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 NP40435. 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/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5. FINANCIAL DISCLOSURE

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

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

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

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

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

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

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

2.1.3. Source Data Records

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

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/EC review. The investigational site must also allow inspection by applicable Health Authorities.

2.1.4. Use of Computerized Systems

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

2.2. RETENTION OF RECORDS

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

2.3. STUDY RECORDS

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

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

2.3.1. Protocol Amendments

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

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients 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/ECs 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 (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

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), which can be found at:

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

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

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

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

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

3.2. ASSESSMENT OF CAUSALITY

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

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

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

4. FOLLOW-UP OF AES AND SAES

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

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

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)
- DLTs during the DLT assessment window (defined in Section 4.1.3; see Appendix 2; Section 5.1 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, NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST AND DOSE-LIMITING TOXICITIES

Events that Occur prior to Study Treatment Initiation

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

Events that Occur after Study Treatment Initiation

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

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

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

Reporting of Post-Study Adverse Events and Serious Adverse Events

After the end of the adverse event reporting period (see Section 8.3.1) all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

5.2. REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

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

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5.1). For RO7121661, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with RO7121661, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

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

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:

- RO7121661 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

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

1.2. OTHER ADVERSE EVENTS

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

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

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

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

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

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

8. PREEXISTING MEDICAL CONDITIONS

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

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

9. LACK OF EFFICACY OR WORSENING OF TUMOR

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST Version 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to progressive disease, it should be reported as an adverse event.

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

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

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

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

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

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

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

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

Appendix 4
Clinical Laboratory Tests

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

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

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

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
Clinical Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, urea or BUN, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH, CRCL (determined by Cockcroft Gault formula)[a], GGT, Magnesium, CRP, ferritin.
Coagulation	Including PT (optional), INR, and aPTT; additional coagulation parameters (i.e., anti thrombin III [antigenic or chromogenic], fibrinogen, PT, fibrin degradation products, D dimer) maybe be assessed according to clinical judgment.
Viral Serology	HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody.
Lipids	Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.
Thyroid Hormones	Free T4, free T3, TSH
Infusion related reactions	IgE and tryptase and cytokine samples will be collected for central and local analysis if a participant experiences a Grade $\geq$ 2 IRR for the first time with the second or subsequent study drug infusion or with clinical signs of hypersensitivity reaction at any time of the conduct of the study. A second sample for central IgE/tryptase analysis will be collected approximately 48 hours after onset of the reaction.
Quantitative Immunoglobulins	IgA, IgG, IgM, IgE
Urinalysis	Specific gravity Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, 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.

Laboratory Assessments	Parameters
Pregnancy Test	All women of childbearing potential (including those who have had a tubal ligation) will have a blood pregnancy test at Screening within 7 days before first dose of study treatment on Cycle 1 Day 1, blood or urine tests during the treatment period (according to the SoA – see Section 1.3), at the discontinuation visit, and at the 60 day (Part A)/90 day (Part B) safety follow up visit. Further blood or 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.
Auto-antibody panel	The auto-antibody panel will be assessed in participants who develop signs and/or symptoms suggestive of auto-immune disease while on-treatment, the auto-antibody panel (anti-nuclear antibody, anti−double-stranded deoxyribonucleic acid (DNA), circulating anti-neutrophil cytoplasmic antibody [cANCA], and perinuclear anti neutrophil cytoplasmic antibody [pANCA]) should be repeated. Patients with confirmed positive serology of at least one of the auto-antibody panel during the course of the study should be discussed between Sponsor and Investigators, and if judged clinically relevant, could be referred to a specialist to exclude an underlying auto-immune disease.
Urinalysis	Specific gravity Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, 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	sCD25

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

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. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

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

a) Pre-menarchal

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

– Documented hysterectomy.

– Documented bilateral salpingectomy.

– Documented bilateral oophorectomy.

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

c) Post-menopausal female

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

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

2. CONTRACEPTION GUIDANCE

- **Female Participants**

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

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

Table 1 Highly Effective Contraceptive Methods

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

• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide [b] • Cap, diaphragm or sponge with spermicide [b]

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

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

b) A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods. i.e., when the risk of teratogenicity and genotoxicity is unlikely.

3. PREGNANCY TESTING

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

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

4. COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5 Pregnancy). This applies only to male participants who receive RO7121661.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with

the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- **Female participants who become pregnant**

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

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

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

5 ABORTIONS

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

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

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

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant or female partner of a male patient 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
Risks Associated with RO7121661 and Guidelines for Management of Adverse Events Associated with RO7121661

Toxicities associated or possibly associated with RO7121661 treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of RO7121661 may not have an immediate therapeutic effect, and in severe cases, immune- mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The Investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of RO7121661. In patients who have met the criteria for permanent discontinuation, resumption of RO7121661 may be considered if the patient is deriving benefit and has fully recovered from the immune- mediated event.

The decision to rechallenge patients with RO7121661 should be based on Investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates may be associated with the administration of RO7121661. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue RO7121661 and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue RO7121661 and contact Medical Monitor. • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The *Investigator determines an* acceptable length of the extended period of time. *T*he Medical Monitor *is available to the Investigator to advise and answer questions in this regard*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

HEPATIC EVENTS

Immune-mediated hepatitis may be associated with the administration of RO7121661. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue RO7121661. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold RO7121661 for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor.

LFT = liver function tests.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue RO7121661 and contact Medical Monitor. • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = liver function tests.

[a] RO7121661 may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

GASTROINTESTINAL EVENTS

Immune-mediated colitis may be associated with the administration of RO7121661. Management guidelines for diarrhea or colitis are provided in Table 3.

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

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

Event	Management
Diarrhea or colitis, Grade 1	• Continue RO7121661. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor.

GI = gastrointestinal.

[a] RO7121661 may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

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

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue RO7121661 and contact Medical Monitor. • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] RO7121661 may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders may be associated with the administration of RO7121661. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue RO7121661. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold RO7121661. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume RO7121661 when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue RO7121661. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold RO7121661. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume RO7121661 when symptoms are controlled and thyroid function is improving. • Permanently discontinue RO7121661 and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume RO7121661. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor.
Hyperglycemia, Grade 1 or 2	• Continue RO7121661. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold RO7121661. • Initiate treatment with insulin. • Monitor for glucose control. • Resume RO7121661 when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue RO7121661 and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue RO7121661. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor.
Ocular event, Grade 3 or 4	• Permanently discontinue RO7121661 and contact Medical Monitor [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] RO7121661 may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

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

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2-4	• Permanently discontinue RO7121661 and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] RO7121661 may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, may be associated with the administration of RO7121661. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 7.

Table 7 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	Amylase and/or lipase > 1.5–2.0 × ULN: • Continue RO7121661. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN: Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor. • For recurrent events, permanently discontinue RO7121661 and contact Medical Monitor.

GI = gastrointestinal.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

Table 7 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor. • For recurrent events, permanently discontinue RO7121661 and contact Medical Monitor.
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue RO7121661 and contact Medical Monitor. • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] RO7121661 may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

DERMATOLOGIC EVENTS

Treatment-emergent rash may be associated with RO7121661. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 8.

Table 8 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue RO7121661. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue RO7121661. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor.
Dermatologic event, Grade 4	• Permanently discontinue RO7121661 and contact Medical Monitor.

[a] RO7121661 may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome may be observed with RO7121661. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 9.

Table 9 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue RO7121661. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor.
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue RO7121661 and contact Medical Monitor. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue RO7121661 and contact Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] RO7121661 may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before RO7121661 can be resumed.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis may be associated with the administration of RO7121661. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

Table 10 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue RO7121661 and contact Medical Monitor. • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

RENAL EVENTS

Immune-mediated nephritis may be associated with the administration of RO7121661. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue RO7121661. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.

Renal event, Grade 2	• Withhold RO7121661 for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor.
Renal event, Grade 3 or 4	• Permanently discontinue RO7121661 and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7121661 can be resumed.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis may be associated with the administration of RO7121661. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue RO7121661. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold RO7121661 for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7121661 can be resumed.

Table 12 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold RO7121661 for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume RO7121661. [b] • If event does not resolve to Grade 1 or better while withholding RO7121661, permanently discontinue RO7121661 and contact Medical Monitor. • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue RO7121661 and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] RO7121661 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. *The Investigator determines an acceptable length of the extended period of time. The Medical Monitor is available to the Investigator to advise and answer questions in this regard.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before RO7121661 can be resumed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Participants with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A participant should be classified as having HLH if five of the following eight criteria are met:

- *Fever ≥ 38.5°C*
- *Splenomegaly*
- *Peripheral blood cytopenia consisting of at least two of the following:*
  - *Hemoglobin < 90 g/L (9 g/dL)*
  - *Platelet count < 100 × 109/L (100 000/μL)*
  - *ANC <1.0 ×10⁹/L (1000/μL)*
- *Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)*
- *Hemophagocytosis in bone marrow, spleen, lymph node, or liver*
- *Low or absent natural killer cell activity*
- *Ferritin > 500 mg/L (500 ng/mL)*
- *Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms*

Participants with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. 2016. A febrile participant should be classified as having MAS if the following criteria are met:

- *Ferritin > 684 mg/L (684 ng/mL)*
- *At least two of the following:*
  - *Platelet count ≤ 181 × 10⁹/L (181,000/μL)*
  - *AST ≥ 48 U/L*
  - *Triglycerides > 1.761 mmol/L (156 mg/dL)*
  - *Fibrinogen ≤ 3.6 g/L (360 mg/dL)*

Participants with suspected HLH or MAS should be treated according to the guidelines in Table 13.

Table 13 *Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome*

Event	*Management*
Suspected HLH or MAS	• *Permanently discontinue study drug and contact Medical Monitor.* • *Consider participant referral to hematologist.* • *Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.* • *Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy.* • *If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.*

HLH = Hemophagocytic lymphohistiocytosis; IV = Intravenous; MAS= Macrophage activation syndrome.

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Appendix 7 New Response Evaluation Criteria in Solid Tumours – 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 CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

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

1.1.2 Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

Bone lesions:

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

1.2.1 Measurement of Lesions

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

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging based evaluation should always be the preferred option.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and $\geq$10 mm diameter as assessed using calipers (e.g., skin nodules). For

the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the subject at baseline and during study, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient 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 above 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 two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved, a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be *reproducible in repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1, 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 two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (see also Section 2.3.4).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. RESPONSE CRITERIA

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$ 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of $<$ 10 mm.

Target lesions that become *'too small to measure'*: while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

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

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

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign <).

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

Progressive Disease (PD): 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 patient 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 patient 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 patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

2.3.5. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing

lesions). This is particularly important when the patient'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. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients 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.

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 patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and during study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient 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.

Best response determination in trials where confirmation of complete or partial response IS NOT required:

Best response is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Best response determination in trials where confirmation of complete or partial response is required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3 Best Overall Response when Confirmation is required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.1 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 patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients 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 patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies where patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

2.5 FREQUENCY OF TUMOR RE-EVALUATION

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

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

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

2.6 CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

2.6.1 Confirmation

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

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

2.6.2 Duration of overall response

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

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

2.6.3 Duration of stable disease

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

3. REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.
2. Bogaerts J, Ford R, Sargent D, et al, Individual patient data analysis to assess modifications to the RECIST criteria Eur J Cancer 2009;45:248-60.

Appendix 8 Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immunotherapy-specific response criteria adaptations to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; Eisenhauer et al 2009) 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 (see Appendix 7) also apply to iRECIST. After disease progression per RECIST v1.1, the same target and non-target lesions selected at baseline will continue to be followed, along with any new lesions that develop, to support iRECIST response evaluations, as described below and summarized in Table 1. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

TARGET LESIONS

The target lesions selected at baseline should continue to be measured at all tumor assessment timepoints after disease progression per RECIST v1.1, according to RECIST v1.1 conventions.

NON-TARGET LESIONS

Non-target lesions selected at baseline should continue to be followed at all tumor assessment timepoints after disease progression per RECIST v1.1. At each timepoint, non-target lesions should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" relative to baseline (progressive disease [PD]), or "present without unequivocal progression" (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non–lymph node lesions must be $\geq$ 10 mm on the longest diameter; new lymph nodes must be $\geq$ 15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint should be measured from that point on, if the maximum number of measurable new lesions has not been reached. However, for calculation of the sum of diameters for new lesions, iRECIST excludes measurements from new lesions that were not measurable at first appearance.

All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$ 10 mm and $<$ 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short

axis of a lymph node is < 10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to < 15 mm (or even < 10 mm).

Table 1 Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1
Target lesions	• Measurements should be continued according to RECIST v1.1 conventions.
Non-target lesions	• Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (PD), or present without unequivocal progression (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.
New lesions	• New lesions should be evaluated for measurability per RECIST v1.1. • All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints. • Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. • All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

CR = complete response; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.

SUMMARY OF CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

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Appendix 9 Correction Formulas for QTc Intervals

Fridericia's correction for QTc Measurement - QTcF

$$QTcF\ (ms) = \frac{QT\ (ms)}{\sqrt[3]{RR(ms)/1000}}$$

Example: QTcF of a subject with a QT of 386 ms and a RR of 848 ms

QT (ms) = 386

RR (ms) = 848

$$\frac{QT\ (ms)}{\sqrt[3]{RR(ms)/1000}} = 408\ ms$$

Bazett's correction for QTc Measurement - QTcB

$$QTcB\ (ms) = \frac{QT\ (ms)}{\sqrt{RR(ms)/1000}}$$

Example: QTcB of a subject with a QT of 386 ms and a RR of 848 ms

QT (ms) = 386

RR (ms) = 848

$$\frac{QT\ (ms)}{\sqrt{RR(ms)/1000}} = 419\ ms$$

Appendix 10 Modified Continuous Reassessment Method with Escalation with Overdose Control Design

This appendix provides details of the design that will guide the monotherapy dose-escalation stage of this study and examines its operating characteristics through simulations. All analyses were performed using the R statistical software R version 3.4.2.

RATIONALE FOR MODEL BASED DESIGN

The modified Continuous Reassessment Method (mCRM) design uses a statistical model that actively seeks a dose level close to the maximum tolerated dose (MTD) by using toxicity data from all enrolled evaluable patients to compute a precise dose-toxicity curve. It locates the MTD efficiently and minimizes the number of patients 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, $\pi(MTD) \in [0.2, 0.35]$ while keeping the probability of overdose $P\{p(MTD) > 0.35\} < 0.25$.

STATISTICAL MODEL

A two-parameter logistic model will be used to fit the dose-toxicity relationship.

The probability of DLT at dose d_j, $p(d_j)$ is defined as (1)

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

where

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

and d^* is the reference dose (in this case d^*=70 mg).

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

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

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

Model Prior

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

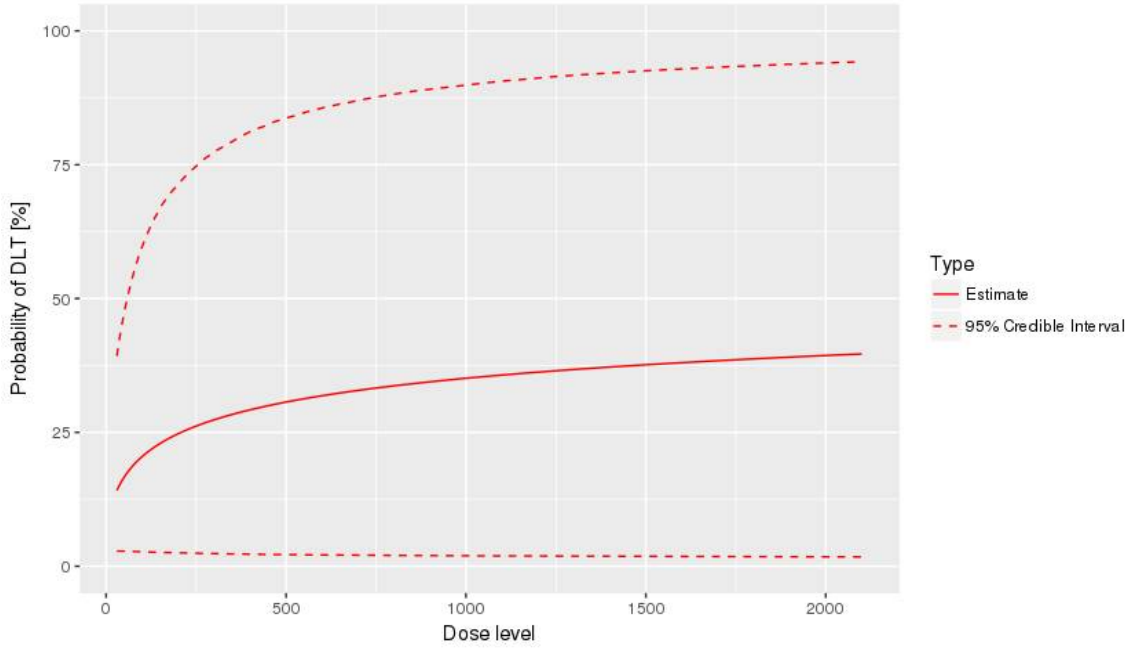
The parameters of the minimal informative prior are listed below (3):

$$\mu = (\alpha, \beta) = (-1.736, 0.326)$$
$$\Sigma = \begin{pmatrix} \sigma_\alpha^2 & \sigma_{\alpha\beta} \\ \sigma_{\alpha\beta} & \sigma_\beta^2 \end{pmatrix} = \begin{pmatrix} 0.8948 & 0.1859 \\ 0.1859 & 0.0747 \end{pmatrix} \quad (3)$$

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

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

Figure 1. Minimally informative prior



Maximum Dose-Increments

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

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

In absence of DLT, the maximum allowable dose-increment will be 200% (i.e. next dose could be as high as 3 fold as previous one) for dose-levels $<$ 700 mg and 100% (i.e. 2 fold) for dose-levels $\geq$ 700 mg

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

In case of one event of DLT in a dose-level, the maximum allowable dose increment becomes 100% (i.e. 2 fold), while in presence of 2 DLTs an increment of 50% is allowed (i.e. 1.5 fold).

After the two rules have been applied the maximum allowed dose increment will be defined as the lower increment of the two resulting increments.

Stopping Rules

The algorithm will recommend stopping the trail if any of the following applies:

- Maximum number of patients: stop if the maximum sample size of 60 pts have been reached OR
- Enough information on MTD: at least a minimum of 12 pts enrolled and at least 6 patients have been accrued near the MTD dose (where near means differing from the MTD by at most 15%) and the probability that the MTD dose lies within the target toxicity interval is above 50% OR
- Maximum dose is safe: at least a minimum of 6 pts have been accrued at the maximum dose or near (differing from the maximum dose by at most 5%) and it is at least 50% likely that the probability of a DLT for that maximum dose is below 20%.

Dose Grid

The following dose grid has been used for the simulations:

- from 30 mg to 100 mg by 2.5
- from 105 mg to 1000 mg by 5
- from 1010 mg to 2100 mg by 10.

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 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, STOP indicates that the model would stop escalating and the trial would be halted.

Table 1. Dose Escalation Mock Runs

		Model recommendation (and % increment) in case of			
Cohort number	**Dose (mg)**	**0 DLT**	**1 DLT**	**2 DLTs**	**3 DLTs**
1	**70**	210 (+200%)	80 (+14%)	35 (-50%)	STOP
2	**210**	615 (+193%)	220 (+5%)	82.5 (-61%)	45 (-79%)
3	**615**	1840 (+199%)	615 (+2%)	225 (-63%)	115 (-81%)
4	**1840**	2100 (+14%)	2050 (+11%)	550 (-70%)	255 (-86%)

As can be seen from the Table above, in general in presence of no DLTs the model will suggest to escalate as the max increments indicate, while in presence of one DLT the increments are really limited. Then, with 2 or 3 DLTs the model always recommends to de-escalate or STOP. Therefore, the results show that the design will adequately adapt the dose in the presence of observed DLTs.

SIMULATION STUDY

A simulation study is conducted to evaluate the operating characteristics for the chosen design parameters (priors, reference dose, stopping rules) under various dose-toxicity scenarios.

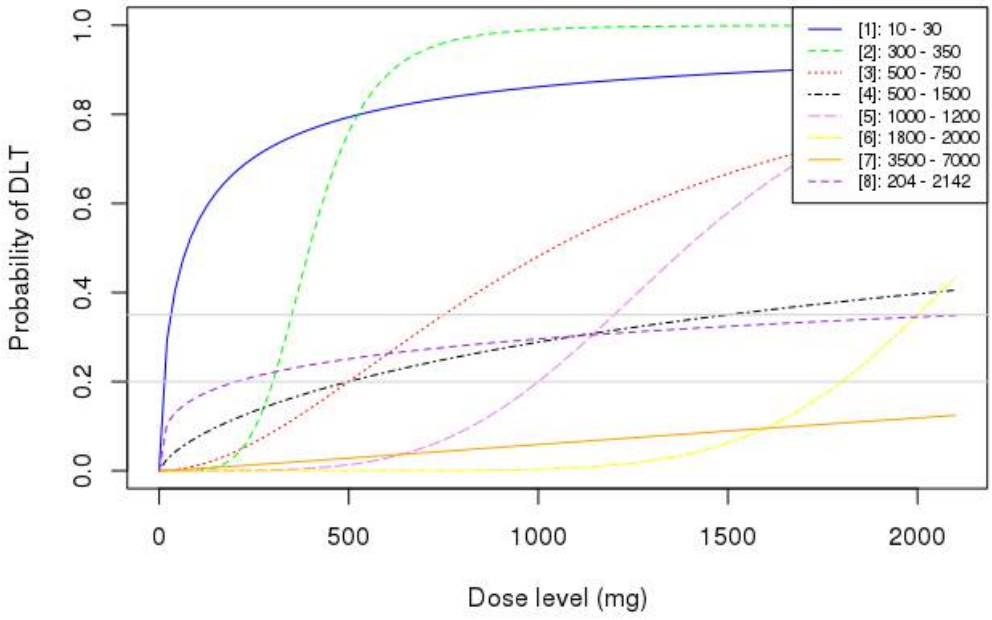
Dose-Toxicity Scenarios

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.

As shown in Figure 2, we explore 8 scenarios. The first 7 represent decreasing levels of toxicity, while the last one considers the toxicity depicted in the prior as true toxicity.

Some scenarios are really extreme, but still they will be informative on how the model would eventually perform, despite the likelihood of the scenario remains extremely low.

Figure 2. True Dose-Toxicity Scenarios: [Scenario number]: dose range corresponding to target toxicity.



Simulation Results

For each of the scenarios, 1000 trials were simulated and in all cases the starting dose of 70 mg was assumed.

The design is evaluated using the following criteria: the MTD chosen, the number of subjects treated at doses higher than the MTD and the total number of subjects treated. For each criterion, we report in Table 2 the median (and 10^{th} 90^{th} percentiles) from the 1000 simulations.

Table 2. Median (and 10^{th} 90^{th} percentiles) from the 1000 simulations

Scenario	Target Dose Interval in True Scenario	Overall N of Patients	N Patients Treated above Target Toxicity Interval	Proportions of DLTs in the trials	Doses selected as MTD
1	**10-30**	6 (3,15)	6 (3,15)	66.7% (41.7%, 100%)	**0** (0,0)
2	**300-350**	21 (15,27)	6 (3,9)	23.8% (19%, 27.8%)	**280** (220,360)
3	**500-750**	24 (18,33)	3 (0,12)	20.8% (18.5%, 25%)	**512.5** (365,765)
4	**500-1500**	27 (24,36)	6 (3,9)	19% (12.3%, 25%)	**572.5** (230,1310)
5	**1000-1200**	27 (24,36)	6 (3,9)	18.5% (16.7%, 22.2%)	**935** (735,1170)
6	**1800-2000**	36 (27,42)	6 (6,12)	12.1% (5.1%, 18.5%)	**2000** (1350,2100)
7	**3500-7000**	39 (30,51)	0 (0,0)	4.2% (0%, 11.1%)	**2100** (2100,2100)
8	**204-2142**	21 (6,39)	0 (0,0)	23.8% (16.7%, 50%)	**215** (0,711)

From these simulations, we see that the design is able to provide a reliable estimate of the MTD: usually, the median of the doses selected as MTD is within the target toxicity dose range. Only in case the toxicity curve is very steep (e.g. Scenario 5) the median might lie just below the target toxicity, which means that we are conservative.

At last, in case of very low toxicity (dose range of target toxicity between 3500 and 7000 mg), the maximum dose is selected as MTD.

In addition, we see that we the number of patients treated over the dose toxicity interval is quite limited, with the exception of the first scenario where –by definition since all doses were too toxic- all pts were treated above the target toxicity.

The good performances of the algorithm are also confirmed by the median number of DLTs observed in the simulations, which is always <25% (again, Scenario 1 is an exception).

Finally, also the sample size required seems to be reasonable: the median number of patients required to give an MTD recommendation is maximum 39 patients across all scenarios. In case of too high toxicity, the required number of treated patients is even lower.

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Schöffski P et al. Phase I trial of intravenous aviscumine (rViscumin) in patients with solid tumors: a study of the European Organization for Research and Treatment of Cancer New Drug Development Group. Annals of Oncology 2004;15: 1816–1824.

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Appendix 11 Exposure Ratios from Nonclinical Safety Findings to Human Exposures

Prediction of human PK followed an allometric scaling approach. Based on first-week DRF and GLP data in cynomolgus monkey, a two-compartment model was developed with additional Michaelis Menten approximation to describe the nonlinear clearance. It is expected that at therapeutically relevant doses, the nonlinear clearance in human is fully saturated. Therefore, the predicted exposures in humans were calculated using the linear PK model only.

The projected $AUC_{0\text{-}336}$ and C_{max} in humans after a single flat dose of 70 mg (corresponding to 1 mg/kg) are 3900 μg·h/mL and 25.2 μg/mL, respectively. These values are approximately 180- and 116-fold lower, respectively, than the exposure observed in cynomolgus monkeys at the 150 mg/kg NOAEL in the 4-week GLP toxicology study (differences in potency i.e., 2-fold more potent in humans than in monkeys and dosing schedule were accounted for).

Prediction of human exposure (C_{max} and $AUC_{0\text{-}336}$) and associated margins as compared to the NOAEL dose level of 150 mg/kg identified in the cynomolgus monkey at steady state (i.e., following eight administrations) are provided in Table 1 (including non-clinical safety findings).

Table 1 Predicted Human Exposures and Associated Margins at Steady State as Compared with the NOAEL Based on NHP GLP Study

Mean Values from 4-week GLP Toxicology and Toxicokinetic Monkey Study after Repeated Weekly Administration			**Simulated Exposure in Human at Steady State[a]**				**Non Clinical Findings at NOAEL in Cynomolgus Monkey**
			70 mg		2100 mg		Marginal, increased incidence and/or severity of inflammatory cell foci/infiltrates in several tissues and organs, no evidence of progression or worsening after recovery, slight increase in IL-10
NOAEL (mg/kg)	C_{max} (μg/mL)	$AUC_{0\text{-}168}$ (μg·h/mL)	C_{max} (μg/mL)	$AUC_{0–336}$ (μg·h/mL)	C_{max} (μg/mL)	$AUC_{0–336}$ (μg·h/mL)	
150	5835	697500	45.2	9200	1355	275000	
Estimated Human Exposure Margins at Steady State[a]			**65x**	**76x**	**2.2x**	**2.5x**	
$AUC_{0\text{-}168/336}$ = area under the concentration–time curve from time 0 to 168/336 hours; C_{max} = maximum concentration observed; NOAEL = no-observed-adverse-effect level; Q2W = every 2 weeks; QW = weekly.							
Notes:							
Cynomolgus monkey: the mean $AUC_{0\text{-}168}$ values are for the recovery animals only after last dosing interval.							
AUC multiples include additional factor of 2 due to different dosing schedule in monkey (QW) and human (Q2W). AUC and C_{max} multiples include additional factor of 2 due to higher expected potency in human compared to monkey.							
[a] Exposure margins = ratios of exposure in monkey/human.							