Official Title: A First in Human, Open Label, Dose Escalation Phase I Study Evaluating Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Clinical Activity Profile of Single Agent RO7119929 (TLR7 Agonist) Administered Orally to Participants with Unresectable Advanced or Metastatic Hepatocellular Carcinoma, Biliary Tract Cancer, or Solid Tumors with Hepatic Metastases

NCT Number: NCT04338685

Document Date: Protocol Version 3: 17-March-2021

PROTOCOL

TITLE:	**A FIRST IN HUMAN, OPEN LABEL, DOSE ESCALATION PHASE I STUDY EVALUATING THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY CLINICAL ACTIVITY PROFILE OF SINGLE AGENT RO7119929 (TLR7 AGONIST) ADMINISTERED ORALLY TO PARTICIPANTS WITH UNRESECTABLE ADVANCED OR METASTATIC HEPATOCELLULAR CARCINOMA, BILIARY TRACT CANCER, OR SOLID TUMORS WITH HEPATIC METASTASES**
PROTOCOL NUMBER:	WP41377
VERSION:	3
EUDRACT NUMBER:	2019-002150-23
IND NUMBER:	To be determined
TEST PRODUCT:	RO7119929
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	12 December 2019
DATE AMENDED:	Version 2: 10 July 2020 Version 3: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
17-Mar-2021 12:52:09	Company Signatory	[redacted]

PROTOCOL ACCEPTANCE FORM

TITLE:	**A FIRST IN HUMAN, OPEN LABEL, DOSE ESCALATION PHASE I STUDY EVALUATING THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY CLINICAL ACTIVITY PROFILE OF SINGLE AGENT RO7119929 (TLR7 AGONIST) ADMINISTERED ORALLY TO PARTICIPANTS WITH UNRESECTABLE ADVANCED OR METASTATIC HEPATOCELLULAR CARCINOMA, BILIARY TRACT CANCER, OR SOLID TUMORS WITH HEPATIC METASTASES**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL AMENDMENT, VERSION 3
RATIONALE

Protocol WP41377 has been amended to introduce additional dosing schedules and to update the cytokine release syndrome (CRS) management guidelines. Changes to the protocol, along with a rationale for each change, are summarized below:

- The original study design has been amended to investigate two alternative dosing schedules for CRS mitigation (step-up dosing [Schedule 2] and flat dosing with tocilizumab pre-treatment [Schedule 3]). The schematic of study design (Section 1.2), the schedules of activities (SoA) tables (Section 1.3), the objectives (Section 3), the description of study design (Section 4), meals and dietary restrictions (Section 5.3.1), the description of tocilizumab administration as pre-treatment (Section 6.1.2), the description of measures to be taken in case of temporary interruption of study treatment (Section 7.1.1), the description of safety analyses (Section 9.4.3), and the statistical model (Appendix 6) have been updated accordingly.
- The SoA has been revised further as follows:
  - Main Table (Section 1.3, Table 1)
    - Addition of requirement for 24-hour hospitalization at specific visits
    - Addition of requirement for mandatory pre-medication in Cycle 1 (details have been included as new Section 6.1.3)
    - Addition of tocilizumab pre-treatment for Schedule 3
    - Additional vital sign monitoring and measurement of oxygen saturation in case of CRS Grade $\geq$2 (footnote 6; details have been added to Section 8 and Section 8.2.2)
    - Clarification that a viral load test for hepatitis B and hepatitis C virus (HBV and HCV) will be performed for all participants at the screening visit (Footnote 20) per local health authority feedback. The related inclusion criterion in Section 5.1 has been modified accordingly.
  - Detailed Tables (Section 1.3, Table 2 and Table 3):
    - Both tables: addition of samples for tocilizumab PK, ADA, and PD markers for the new Schedule 3 with tocilizumab pre-treatment
    - Addition of sampling timepoints for RO7119929 PK and PD markers based on the observed PD and safety cytokine profile and kinetics
      - Table 2: PK plasma, PD plasma (safety), PD plasma, and PD blood (RNA) added to Cycle 1, Day 15 at predose, 2 and 8 hours after dosing and to Cycle 2, Day 1 at 12 hours after dosing
      - Table 3: PK plasma, PD plasma (safety), PD plasma, and PD blood (RNA) added to Cycle 1, Day 15 at predose, 2 and 8 hours after dosing and to Cycle 2, Day 1 at 12 hours after dosing

    - Both tables: removal of PD plasma (safety) sample at 30 hours after dosing from Cycle 1, Day 2 and Cycle 2, Day 2
    - Both tables: addition of a PD blood (RNA) sample at unscheduled visits.
    - Both tables: clarification that only the assessments for an unscheduled visit need to be performed if the EOTV/EDV coincides with an unscheduled visit.
    - Table 2 only: Clarification that in case no drug is administered on C2D1, all assessments planned for that day will be delayed to after the next drug administration.
  - Detailed tables for step-up dosing have been added (Table 4 and Table 5)
- A discussion of risks associated with SARS-Cov-2 infection has been added to Section 2.3 (Benefit/Risk Assessment)
- The eligibility criteria (Section 5.1 and Section 5.2) have been updated to optimize the participant population based on emerging data as follows:
  - The definition for the inclusion criterion “adequate hematologic function” has been amended to include a hemoglobin value of ≥9.0 g/dL (instead of 10.0 g/dL) in the absence of impaired hematological function in the study participants treated so far.
  - For participants with HCC, the inclusion criterion based on Child-Pugh score has been changed from “B7 or better” to “A6 or better” to reflect the fragility of patients with Child-Pugh score of B7 and align with the overall eligibility criteria of the study.
  - It has been clarified that only major surgery within 3 weeks of dosing is an exclusion criterion.
  - The exclusion of HCV-RNA positive participants has been limited to HBV co-infected participants in line with the high unmet medical need in the HCV-positive HCC patient population, the positive benefit risk assessment for this population with other cancer immunotherapies and the absence of exacerbations of infections in the study participants treated so far.
  - It has been clarified that vaccination with a live or live-attenuated vaccine within 28 days prior to Day 1 is an exclusion criterion.
- Section 6.1.2 and Footnote 1 below Table 8 in Section 6.1 about use of locally available (commercial) tocilizumab in emergency situations have been updated to clarify that this is only applicable where approved locally.
- Details regarding timing of preventive/routine vaccinations before and during the study have been added to Section 6.5.3 (Prohibited Therapy) to allow for preventive vaccinations with the exception of live and live-attenuated vaccines.
- Section 6.6. (Dose Modification) has been revised for consistency with Section 4.1.1.1 (Description of Study Part A) to allow re-treatment of participants with a DLT at a reduced dose and following regression of toxicity in agreement with the Sponsor.

- The guidelines for managing specific adverse events (Section 8.3.9) have been modified based on emerging data related to the safety profile of RO7119929.
- Section 8.8.1.3 was amended to clarify that it is mandatory to obtain formalin-fixed paraffin embedded archival tumor tissue from all participants (minimum of 4 slides recommended if blocks are not available).

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
BTC	Biliary tract cancer
CIT	Cancer immunotherapy
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum concentration
CNS	Central nervous system
COA	Clinical outcome assessments
COVID-19	Coronavirus disease 2019
CPI	Checkpoint inhibitor
CR	Complete response
CRC	Colorectal cancer
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DCR	Disease control rate
DLT	Dose-limiting toxicities
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eCOA	Electronic clinical outcome assessment
EOTV	End of treatment visit
EU	European Union
EWOC	Escalation with overdose control

FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GC	Gastric cancer
GRIm	Gustave Roussy Immune
HBsAg	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
HIV	Human immunodeficiency virus
iCC	Intrahepatic cholangiocarcinoma
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
iRECIST	immune Response evaluation criteria in solid tumors
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
LPLV	Last participant, last visit
LVEF	Left ventricular ejection fraction
MoA	Mode of action
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NGS	Next generation sequencing
NIMP	Non-investigational medicinal product
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
OBD	Optimal biological dose
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD	Pharmacodynamic
PD-1	Anti-programmed death

PD-L1	Anti-programmed death-ligand
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PK	Pharmacokinetic
PoM	Proof of mechanism
PR	Partial response
PT	Prothrombin time
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
QW	Weekly
RBC	Red blood cell
RBR	Research biosample repository
RCC	Renal cell carcinoma
RDE	Recommended dose for expansion
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RR	RR interval
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of activities
TLR	Toll-like receptor
t_{max}	Time of maximum concentration observed
TME	Tumor microenvironment
TNBC	Triple negative breast cancer
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
V	Volume
WBC	White blood cell
WES	Whole exome sequencing
WGS	Whole genome sequencing
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A FIRST IN HUMAN, OPEN LABEL, DOSE ESCALATION PHASE I STUDY EVALUATING THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY CLINICAL ACTIVITY PROFILE OF SINGLE AGENT RO7119929 (TLR7 AGONIST) ADMINISTERED ORALLY TO PARTICIPANTS WITH UNRESECTABLE ADVANCED OR METASTATIC HEPATOCELLULAR CARCINOMA, BILIARY TRACT CANCER, OR SOLID TUMORS WITH HEPATIC METASTASES**
SHORT TITLE	**A PHASE I STUDY EVALUATING SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND CLINICAL ACTIVITY OF RO7119929 (TLR7 AGONIST) IN PARTICIPANTS WITH UNRESECTABLE ADVANCED OR METASTATIC HEPATOCELLULAR CARCINOMA, BILIARY TRACT CANCER, OR SOLID TUMORS WITH HEPATIC METASTASES**
PROTOCOL NUMBER:	WP41377
VERSION:	*3*
TEST PRODUCT:	RO7119929
PHASE:	I

RATIONALE

The management of most advanced solid tumors remains challenging as only a small proportion of patients responds to standard of care therapy, and almost all patients progress on or after therapy. Cancer immunotherapy (CIT) with immune checkpoint inhibiting (CPI) monoclonal antibodies such as anti-programmed death-1 (PD-1)/anti-programmed death-ligand 1 (PD-L1), has changed the treatment landscape in many cancer types, however, a majority of patients with metastatic disease do not derive benefit from this type of CIT, particularly those with non-inflamed (immune deserted or immune excluded) tumors.

Toll-like receptor (TLR) 7 is a member of the TLR family, which encompasses a group of major regulators of the innate immune response. TLR7 is an endosomal sensor of single-stranded RNA mainly expressed in hematopoietic cells, including plasmacytoid dendritic cells, macrophages, and B cells. TLR7 signals through MyD88, which results in a cytokine response (mainly IFN-α) and may promote an inflammatory microenvironment to foster effector T-cell activation and subsequent anti-tumor immunity. Multiple TLR7 agonists have entered clinical development for

various tumor types. To date, their efficacy in early phase clinical studies has been hampered by several issues, including poor tolerability due to strong systemic cytokine activation.

RO7119929 is an orally administered prodrug of a TLR7 agonist. Conversion of RO7119929 to the active drug RO7117418 is mainly mediated through CYP2C9 and CYP2C19 metabolism. A predominantly hepatic activation is anticipated, based on the expression profile of these cytochromes as well as in vitro data generated in human hepatocytes and enterocytes demonstrating selective conversion in the liver. Together with a low solubility of the active drug RO7117418, this supports a rationale for evaluating tumors with predominant hepatic localization. The orally available prodrug approach may allow for an effective TLR7-mediated reprogramming of the immune microenvironment in the liver while limiting systemic immune effects.

WP41377 is a phase I study of RO7119929 given orally to participants with unresectable advanced or metastatic primary liver cancers and other solid tumors with predominant liver involvement. The primary objective of the study is to explore the safety and to determine the maximum tolerated dose (MTD) and/or optimal biologic dose (OBD of RO7119929 as single agent.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate safety and tolerability of RO7119929 (prodrug) in participants with solid tumors with predominant liver involvement *with and without tocilizumab pre-treatment* • To determine the maximum tolerated dose (MTD) and/or optimal biologic dose (OBD) for RO7119929 *with and without tocilizumab pre-treatment*	• Nature and frequency of dose-limiting toxicities • Incidence, nature and severity of adverse event according to NCI CTCAE v5.0
Secondary	
• To evaluate the PK profile of RO7119929 and RO7117418 (active drug) following oral administration of RO7119929 in participants with solid tumors with predominant liver involvement • To evaluate the effect of food on pharmacokinetics of RO7119929 and RO7117418 after administration of RO7119929 in participants with solid tumors with predominant liver involvement	• PK parameters such as C_{max}, T_{max}, AUC, $T_{1/2}$ for RO7119929 and RO7117418 following administration of RO7119929 • Effect of a meal on PK parameters such as C_{max}, T_{max}, AUC, $T_{1/2}$ for RO7119929 and RO7117418 following administration of RO7119929 compared to fasting conditions
• To evaluate peripheral blood for biomarkers to support optimal biological dose and schedule selection	• Change in inflammatory PD biomarkers in peripheral blood such as IFN-α and ISGs.

Objectives	Endpoints
• To assess preliminary clinical activity of RO7119929 administration in participants with solid tumors with predominant liver involvement	• Objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DOR) • Progression-free survival All of the above will be evaluated according to RECIST v1.1. • Overall survival
• To assess preliminary clinical activity signals of RO7119929 administration in participants with solid tumors with predominant liver involvement with respect to liver lesions only	• ORR • DCR • DOR All of the above will be evaluated according to RECIST v1.1 and with respect to responses in liver lesions only.

OVERALL DESIGN

Study Design

WP41377 is a first in human, open label, multi-center, multiple-ascending dose escalation, Phase I study consisting of two parts: Part A (dose-escalation) and Part B (dose expansion). *In addition, the effect of food intake on the pharmacokinetics (PK) of RO7119929 will be investigated.*

RO7119929 will be administered weekly (QW) in 3-week cycles. Within Part A, three different schedules will be investigated: Schedule 1 (QW flat dosing), Schedule 2 (QW step-up dosing), and Schedule 3 (QW flat dosing with tocilizumab pre-treatment). Other treatment schedules may be explored, based on emerging data after amending the protocol accordingly. *Part B may enroll up to three expansion cohorts at different doses and / or dosing schedules based on emerging clinical and pharmacodynamic (PD) data.*

If dose escalation cohorts (Part A) and dose expansion cohorts (Part B) are open in parallel, the Sponsor will decide where to enroll each participant. Depending on evolving data, these decisions might aim at enrichment of certain participant subgroups within the PD expansion cohorts, e.g., by selection for certain tumor types.

If two or more dose expansion cohorts are open in parallel, enrollment into these cohorts will be decided by randomization.

Part A of this study will define the MTD/recommended dose for expansion (RDE) *for different dosing schedules* by escalating doses of RO7119929 as a single agent in adult patients with advanced or metastatic solid tumors with predominant liver involvement. Following determination of MTD and/or RDE, treatment will commence *in Part B or this study* at up to three different doses *and/or dosing schedules* in specific expansion cohorts of participants for extended PD analysis, including collection of peripheral blood and mandatory paired tumor biopsies taken from the hepatic tumor manifestations to demonstrate proof of mechanism (PoM) .

Treatment Groups and Duration

The investigational medicinal products (IMPs) are: RO7119929 (capsule, oral administration) and tocilizumab (IV).

Pre-medication for RO7119929

At Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15, the participant should be pre-medicated with 500 mL of crystalloid fluid and 500-1000 mg paracetamol orally (PO) or intravenously (IV) at the time of RO7119929 administration (± 30 minutes), followed by 500-1000 mg paracetamol PO or IV 4-6 hours after first drug administration. If no cytokine release syndrome (CRS) is observed, no further pre-medication is foreseen beyond Cycle 1.

Pre-medication for participants who experience a Grade ≥2 CRS is to be administered for the subsequent dose according to the adverse event (AE) management guidelines.

The pre-medication regimens are based on the expected duration of inflammatory events and may be modified based on emerging data.

The treatment groups in the two parts are as follows:

Study Part A (Dose-Escalation)

Within Schedule 1 and Schedule 3, RO7119929 will be administered QW at the same dose. Within Schedule 2, RO7119929 will be administered QW with step-up dosing during Cycle 1. Within Schedule 3, tocilizumab will be administered as pre-treatment on Cycle 1 Day 1, approximately 2 hours prior to RO7119929 administration.

Participants will be enrolled in cohorts with at least 3 evaluable participants, treated in a staggered manner (at least 1 week between the first and second participant and at least 24 hours between subsequent participants).

Treatment will consist of a screening period (Day -28 to Day -1), a treatment period (Cycle 1 Day 1 to month 12; the length of the study may be modified based on emerging data), a time period following treatment discontinuation (concluded by an end of treatment visit [EOTV] within 28 days of last study drug, followed by a safety follow-up visit 60 days after last study drug), and post-treatment survival follow-up assessments every 3 months for up to 24 months. Safety assessments for dose-limiting toxicity (DLT) determination will be performed during the first 3 weeks (21 days) *or 4 weeks (28 days) depending on schedule.* Drug administration during the treatment period will continue until disease progression, unacceptable toxicities, or withdrawal of the participant's consent up to a maximum of 12 months or 17 cycles, whichever comes first. As with other immunotherapies, treatment beyond progressive disease according to the response evaluation criteria in solid tumors (RECIST) v1.1 can be considered if deemed in the best interest of the study participant.

Dose escalation will be carried out according to a modified continual reassessment method (mCRM) with overdose control (mCRM-EWOC design). Dose escalation decisions and selection of the dose for the next cohort will be subject to clinical judgement by the Sponsor and the participating Investigators following review of all safety and available pharmacokinetic (PK and/or PD data and not based solely on DLT information, while being guided by the CRM-EWOC recommendation.

For exploring the effect of food intake on the PK of RO7119929 *in Part A, participants* will receive RO7119929 after a defined meal at *the time of first target dose (*Cycle 1 Day 1 *or Cycle 1 Day 15, depending on schedule)* and following a 10-hour fast at Cycle 2 Day 1 enabling intra-participant comparison. For this pilot food effect (FE) study, a minimum of 6 evaluable participants will be enrolled across several cohorts.

Study Part B (Dose Expansion)

Each expansion cohort will enroll approximately 10 PD-evaluable participants. Participants with both available and evaluable tumor biopsy samples will be considered evaluable for the PD endpoint. If signs of relevant anti-tumor and/or PD activity are observed within Part A at dose levels below MTD, it may be decided to initiate Part B at this dose level *and schedule (i.e., 1, 2, or 3)* before Part A is complete after discussion and alignment between the Investigators and the Sponsor.

Treatment for all participants in Part B will consist of a screening period (Day -28 to Day -1), a treatment period (Cycle 1 Day 1 to month 12), a treatment discontinuation period (within 28 days of last study drug until EOTV), one safety follow-up visit and post-treatment survival follow-up assessments. Drug administration during the treatment period will continue until disease progression, unacceptable toxicities, or withdrawal of the participant's consent up to a maximum of 12 months. As with other immunotherapies, treatment beyond progressive disease according to RECIST v1.1 can be considered, if deemed in best interest of the study participant.

The effect of food intake on PK data *may* be explored within Part B *if less than* 6 evaluable participants *were included in* Part A.

Management of Cytokine Release Syndrome

Consistent with the TLR7 mechanism of action, cytokine release syndrome (CRS) has been reported with other systemic TLR7 agonists and IFN-α therapy. *In this study tocilizumab will be*

administered as pre-treatment in Schedule 3. In addition, it can be used to manage CRS associated with RO7119929 in all study schedules. The efficacy of tocilizumab in the management of a potential CRS associated with RO7119929 is unknown. Hence, tocilizumab should be used *for treatment of CSR* only after careful consideration of the benefit/risk in a given participant.

Length of Study

Approximately 14 months (screening phase 28 days, treatment period up to 12 months, and follow-up period 28 days)

End of Study

The end of this study is defined as the date when the last participant, last visit occurs or after approximately 14 months after the last participant is enrolled, whichever occurs first. For an individual participant, the completion of the study (i.e., the last visit) will occur when the participant withdraws consent, has been lost to follow-up, dies, or when the study is stopped. Because of the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor.

Data Monitoring Committee: No

PARTICIPANT POPULATION

This study will enroll adults with unresectable advanced or metastatic hepatocellular carcinoma (HCC), biliary tract cancer (BTC), or specific solid tumors with predominant liver involvement.

Key Inclusion Criteria

- Histologically confirmed diagnosis of one of the following:
    - Participants with unresectable advanced or metastatic HCC (including fibrolamellar HCC) not amenable to a curative treatment approach. For participants with cirrhosis, clinical diagnosis by the American Association for the Study of Liver Diseases (AASLD) criteria is sufficient.
    - Participants with unresectable advanced or metastatic intrahepatic or perihilar (Klatskin) BTC not amenable to a curative treatment approach.
    - Participants with extrahepatic BTC or gallbladder cancer infiltrating the liver or metastasized into the liver with predominant liver disease, not amenable to a curative treatment approach.
    - Participants with metastasized colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), Gastric cancer (GC), renal cell carcinoma (RCC), triple negative breast cancer (TNBC), cutaneous melanoma, or ocular melanoma with predominant liver disease not amenable to a curative treatment approach. Participants with other solid tumors with predominant liver disease not amenable to a curative treatment approach might be enrolled after Sponsor approval.
- Measurable disease with at least one measurable locally untreated liver lesion, as defined by RECIST v1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Adequate hematologic function.
- Adequate major organ functions.
- Participants for which there is no available standard therapy likely to confer clinical benefit, or participants who are not candidates for such available therapy.
- Life expectancy of ≥12 weeks, approximated with Royal Marsden Hospital score 0-1 or Gustave Roussy Immune (GRIm) score 0-1. Participants with a Royal Marsden Hospital or GRIm score of ≥2 and a life expectancy of ≥12 weeks according to the investigator's clinical judgement may be enrolled after Medical Monitor approval has been obtained.
- For participants with HCC: Child-Pugh score of *A6* or better.

Key Exclusion Criteria

- History or clinical evidence of central nervous system (CNS) primary tumors or metastases including leptomeningeal metastases, unless they have been previously treated, are asymptomatic, and have had no requirement for steroids or enzyme-inducing anticonvulsants in the last 14 days prior to Screening.
- Evidence of any extra-hepatic primary tumor or metastasis requiring prompt medical intervention.
- Receipt of prior therapy with a TLR7/8/9 agonist and/or IFN-α.
- Prior chemotherapy, antibody, or other registered or experimental cancer treatment within 3 weeks of study Cycle 1 Day 1. Specifically, no CPI antibody is allowed to be administered within 6 weeks of study Cycle 1 Day 1.
- Receipt of investigational agent for any other indication within 3 weeks of dosing.
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment.
- Local therapy to liver (e.g. radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, and transarterial embolization) within 3 weeks prior to initiation of study treatment, radioembolization within 3 months prior to initiation of study treatment, or non-recovery from side effects of such procedure.
- Treatment-related toxicities from prior cancer therapy that have not resolved to $\leq$ Grade 1 CTC AE prior to study treatment with the exception of the following Grade 2 toxicities: alopecia, peripheral neuropathy, any laboratory changes that still lie within the inclusion criteria defined above.
- History of other malignancy within 2 years; exception for ductal carcinoma in situ not requiring chemotherapy, low grade cervical intraepithelial neoplasia (CIN), non-melanoma skin cancer, low grade localized prostate cancer (Gleason score $<$ Grade 7), or optimally treated Stage 1 uterine cancer.
- Active or history of immunologic-mediated disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjogren's syndrome or Guillain-Barré syndrome.
- *History of human immunodeficiency virus (HIV) infection*
- *Active hepatitis B virus (HBV) infection*
- *Coinfection of HBV and hepatitis C virus (HCV).*

NUMBER OF PARTICIPANTS

Approximately 35 to 40 evaluable participants will be included *under each schedule for* dose escalation Part A. The exact number of participants will depend on the occurrence of DLTs and the number of dose-levels required to determine the MTD and/or the RDE.

Up to approximately 60 participants will be enrolled in the study expansion Part B.

CONCOMITANT MEDICATIONS

RO7119929 might inhibit CYP3A in the gastro-intestinal tract during its absorption. Co-medications known to be moderate and strong CYP3A substrates should be therefore administered at least 4 hours before and 2 hours after RO7119929 in order to minimize the risk of increased exposure of these co-medications.

Co-medications known to interfere with CYP2C9 and CYP2C19 by moderate and strong inhibition are generally prohibited as they might inhibit the conversion of RO7119929 during first pass but might be allowed after discussion with the Sponsor.

Co-medications known to be OATP substrates/inhibitors should be administered at least 4 hours before and 8 hours after RO7119929.

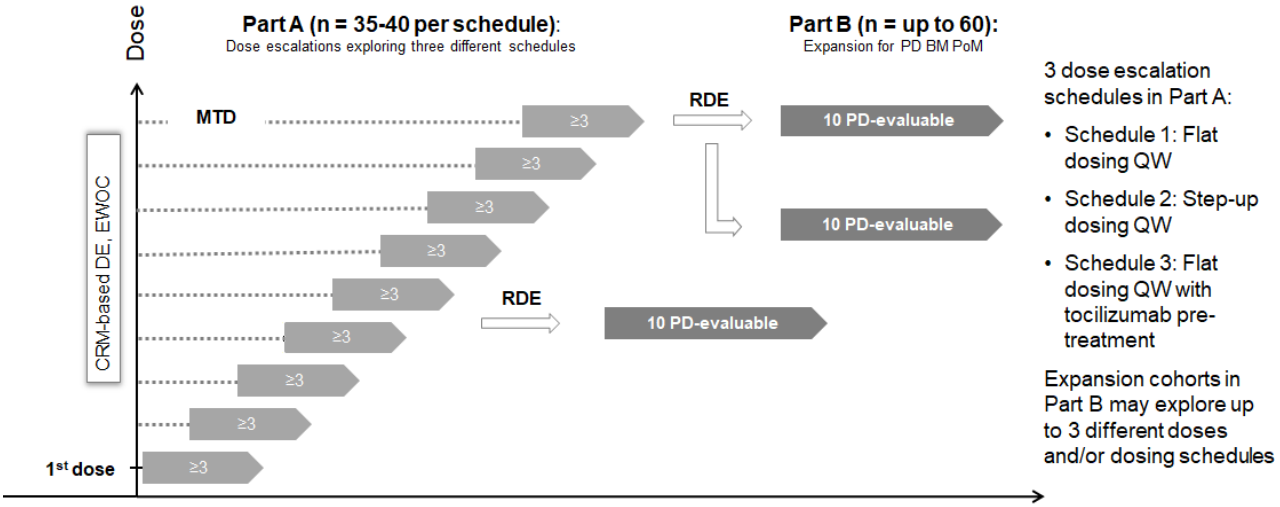
Co-medication known to be UGT1A9 and UGT1A1/1A3 inhibitors might increase the exposure of the active drug RO7117418 and should therefore be administered at least 4 hours before and 8 hours after RO7119929.

The use of systemic anti-cancer therapy is prohibited during the study and for at least 21 days prior to initiation of study treatment, unless otherwise specified.

1.2 SCHEMATIC OF STUDY DESIGN

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

Figure 1 Overview of Study Design – Monotherapy Dose-Escalation and Pharmacodynamics Dose Expansion



BM=Biomarker; *CRM=Continual reassessment method;* DE=Dose-escalation; EWOC=Escalation with overdose control; MTD=Maximum tolerated dose; PD=Pharmacodynamic; PoM=Proof of mechanism; QW=Weekly; RDE=Recommended dose for expansion.

1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities (SoA) *is* provided in Table 1. *Pharmacokinetic and pharmacodynamic measurements for the dose escalation (Part A) and dose expansion (Part B) are provided in*

- Table 2 - *detailed table for pharmacokinetic and pharmacodynamic measurements for dose escalation with flat dosing in Part A Schedule 1 (without tocilizumab pre-treatment) and Part A Schedule 3 (with tocilizumab pre-treatment)*
- Table 3 - *detailed table for pharmacokinetic and pharmacodynamic measurements for dose expansion with flat dosing in Part B Schedule 1 (without tocilizumab pre-treatment) and Part B Schedule 3 (with tocilizumab pre-treatment)*
- *Table 4 - detailed table for pharmacokinetic and pharmacodynamic measurements for dose escalation with step-up dosing in Part A Schedule 2*
- *Table 5 – detailed table for pharmacokinetic and pharmacodynamic measurements for dose expansion with step-up dosing in Part B Schedule 2*

Table 1 Schedule of Activities for Part A and Part B

Cycle (21 Days)	Screening/Baseline	Cycles 1-2				Cycles 3-4			Cycles 5+	EOTV or EDV	Safety follow-up visit	Long-term follow-up assessment
Day[1]	D-28 to D-1	D 1	D 2	D 8	D 15	D 1	D 8	D 15	D 1	Within 28 days after last study drug	60 days after last study drug	Every 90 days after last study drug
Time window			±2 h[2]	±1 d	±1 d	±1 d	±1 d	±1 d	±2 d		± 5 d	± 7 d
Eligibility and informed consent	x											
Medical history[3]	x											
Physical examination[4,5]	x	x		x	x	x			x	x	x	
Vital signs[6]	x	x	x	x	x	x	x	x	x	x	x	
24-h hospitalization for Schedules 1 and 3[7]		x										
24-h hospitalization for Schedule 2[7]		x			x							
Height (at screening only) and weight	x	x				x			x	x	x	
ECOG performance status[5]	x	x				x			x	x	x	
Triplicate 12-lead ECG[8]	x	x		x	x	x			x	x	x	
Echocardiogram/MUGA[9,10]	x					x			x	x		
Eye examination[10, 11]	x								x	x		
EGD (participants with HCC only) [12]	x											
Child-Pugh Score (participants with HCC only)	x											
Hematology[5,10,13]	x within D-7 and D-1	x		x	x	x	x	x	x	x	x	
Serum chemistry[5,10,14]	x	x	x	x	x	x	x	x	x	x	x	
Myocardial markers[5,10,15]	x	x				x			x	x	x	
Coagulation (INR, PT, and aPTT)[5,10]	x	x		x	x	x	x	x	x	x	x	
Thyroid function[5,10,16]	x								x	x		
AFP testing (participants with HCC only)[5,10]		x				x			x	x	x	
Autoimmune panel[5,10,17]	x									x		
Urinalysis (glucose, protein, and urobilinogen)[5,10]	x	x[18]				x[18]			x[18]	x	x	

Table 1 Schedule of Activities for Part A and Part B (cont.)

Cycle (21 Days)	Screening/Baseline	Cycles 1-2				Cycles 3-4			Cycles 5+	EOTV or EDV	Safety follow-up visit	Long-term follow-up assessment
Day[1]	**D-28 to D-1**	**D 1**	**D 2**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**Within 28 days after last study drug**	**60 days after last study drug**	**Every 90 days after last study drug**
Time window			±2 h[2]	±1 d	±1 d	±1 d	±1 d	±1 d	±2 d		± 5 d	± 7 d
HIV, hepatitis B/C serology [5,10,19]	x									x		
HBV, HCV viral load[20]	x	x							x	x	x	
Pregnancy testing[21]	x	x				x			x	x		
Radiological tumor assessment[10]	x	Every 6 weeks following initiation of study treatment[22]								x		
RO7119929 administration[23]		x		x	x	x	x	x	x[24]			
Pre-medication (Cycle 1 only)		x		x	x							
Tocilizumab pre-treatment for Schedule 3[25]		x			(x)							
PK and PD/biomarker blood samples (Part A and B), and fresh tumor biopsies (Part B)	**see Table 2 for Part A - Schedules 1 and 3, Table 3 for Part B Schedules 1 and 3, Table 4 for Part A Schedule 2, and Table 5 for Part B Schedule 2**											
Archival tumor tissue	x[26]											
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x[27]
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	
Anti-cancer therapies[28]											x	x
Survival[28]												x

AFP=Alpha-fetoprotein; aPTT=Activated partial thromboplastin time; *C=cycle*; CRS= Cytokine release syndrome; d/D=day; ECG=Electrocardiogram; ECOG= Eastern Cooperative Oncology Group; *eCRF=electronic case report form;* EGD=esophagogastroduodenoscopy; EOTV=End of Treatment Visit; EDV=Early Discontinuation Visit; *HBV=hepatitis B virus, HCC=hepatocellular carcinoma; HCV=hepatitis C virus;* HIV= Human immunodeficiency virus; h=hours; INR=International normalized ration; MUGA= Multigated acquisition scan; PD=Pharmacodynamic; PK=Pharmacokinetic; PT=Prothrombin time.

Table 1 Schedule of Activities for Part A and Part B (cont.)

1. Clinic visits are completed at the specified time points. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled visit, an unscheduled visit should be performed. For PK and PD measurements during unscheduled visits, see Table 2 *for Part A Schedules 1 and 3,* Table 3 *for Part B Schedules 1 and 3, Table 4 for Part A Schedule 2, and Table 5 for Part B Schedule 2.*
2. The assessments on D2 will be performed 24 h after drug administration on D1, with a time window of ± 2 h.
3. Medical history includes: demographics, history of malignancy, previous treatment(s) for malignancy, concomitant diseases, previous surgeries, medication, allergies, reproductive status, alcohol consumption, and smoking habits.
4. Assessments include: cardiovascular, respiratory, gastrointestinal, dermatological, neurological, and musculoskeletal systems and head, eyes, ears, nose, throat, neck and lymph nodes. Examination of other body systems may be performed at the Investigator's discretion. New or worsened abnormalities should be recorded as AEs, if appropriate.
5. Limited physical examination and local laboratory assessments may be obtained ≤48 hours before Day 1/8/15 of each cycle, if applicable. Local laboratory assessments must be reviewed prior to study treatment administration for each cycle.
6. Obtain vital signs *(systolic and diastolic blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation)*
   For Schedules 1 and 3:
   during C1D1: Pre-dose (within 2h), 0.25h, 0.5h (both ±5 min), 1h, 1.5h, 2h, 3h, 4h (all ±15 min), 5h, 6h, 7h, 8h, 12h, 16h, 20h (all ± 30 min), 24h (±2h);
   during C1D8, D15 and C2D1: Pre-dose (within 2h), 1h, 2h, 3h, 4h (all ±15 min), 5h, 6h, 7h, 8h (all ±30 min);
   during **C2D8, D15 and Cycles 3 and 4, Days 1, 8, and 15**: Pre-dose (within 2h), 1h, 2h (both ±15 min).
   *In case of a second administration of prophylactic tocilizumab at C1D15, vital signs during **C2D8** need to be obtained as follows: Pre-dose (within 2h), 1h, 2h, 3h, 4h (all ±15 min), 5h, 6h, 7h, 8h (all ±30 min).*
   For Schedule 2:
   ***during C1D1, C1D8, C2D1 and C2D15**: Pre-dose (within 2h), 1h, 2h, 3h, 4h (all ±15 min), 5h, 6h, 7h, 8h (all ±30 min);*
   ***during C1D15**: Pre-dose (within 2h), 0.25h, 0.5h (both ±5 min), 1h, 1.5h, 2h, 3h, 4h (all ±15 min), 5h, 6h, 7h, 8h, 12h, 16h, 20h (all ±30 min), 24h (±2h);*
   ***during C2D8 and Cycles 3 and 4, Days 1, 8, and 15**: Pre-dose (within 2h), 1h, 2h (both ±15 min).*
   For all Schedules:
   For all following visits, vital signs should be measured pre-dose, if applicable.
   Additional monitoring may be required in case of CRS (see Section 8.3.9).
   Oxygen saturation needs to be reported in addition to the other vital signs in case of CRS Grade ≥2 until complete resolution of symptoms or discharge of participant, whatever happens first.
7. *Mandatory 24-hour hospitalization: for Schedules 1 and 3 at C1D1 and C2D1; for Schedule 2 at C1D15 and C2D1.*
8. ECGs to be obtained: At screening, during C1D1, D8 and D15 and C2D1: pre-dose (within 2h), 1h, 2h, 4h (all ± 15 min) and 8h (± 30 min). For all following cycles, Day 1: pre-dose (within 2h). EOTV/EDV, Safety F/U. ECGs should be performed prior to blood draws for PK/PD samples at the same time point. Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur.
9. Echocardiogram/MUGA to evaluate left ventricular ejection fraction (LVEF) will be performed during screening, at C3D1, at C5D1, and at EOTV/EDV. The acceptable time window is ± 1 week for on-treatment and end-of-treatment assessments. Does not need to be repeated at EOTV/EDV, if last echocardiogram/MUGA was performed within six weeks before visit. Additional unscheduled echocardiogram/MUGA assessments should be performed in case of abnormalities and if clinical symptoms occur. In case a MUGA scan is performed, the scan must be performed at least 3 days prior to C1D1 and 3 days prior to the tumor biopsy to allow collection and immediate shipments of sensitive PD/biomarker samples (i.e. tumor biopsies, PD whole blood FACS).

Table 1 Schedule of Activities for Part A and Part B (cont.)

10. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and per protocol relevant window may be used for screening assessments rather than repeating such tests. Screening local laboratory assessments obtained ≤96 hours prior to the initiation of study treatment do not have to be repeated for C1D1. Test results should be reviewed prior to administration of study treatment.
11. Ophthalmological evaluation, including medical history (applicable at baseline) and physical examination related to eye disorders, visual acuity, visual field testing, and ophthalmoscopy (including dilated fundoscopy), will be performed during screening, every 3 months thereafter while participants are on treatment, at EOTV/EDV, and as clinically indicated. The acceptable time window is ±2 weeks for on-treatment and end-of-treatment assessments. The examination does not need to be repeated at EOTV/EDV, if the last examination was performed within six weeks before visit.
12. For participants with HCC, an EGD should be performed to assess all size of varices (small to large) and to treat those per local standard of care prior to enrollment. Participants who have undergone an EGD within 6 months prior to initiation of study treatment do not need to repeat the procedure.
13. Complete blood count including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count.
14. Serum chemistry panel includes: total protein, albumin, total and direct bilirubin, AST, ALT, ALP, lipase, LDH, BUN or urea, creatinine, urate, CRP, calcium, phosphate, glucose, sodium, potassium, magnesium, bicarbonate and chloride.
    For Schedule 2 only:
    Serum chemistry panel not rquired at C1D2.
15. Myocardial markers will be measured at Screening, C1D1, C2D1, C3D1, C4D1, C5D1, EOTV/EDV, Safety F/U and when clinically indicated and include cardiac troponin I (cTnI) or cardiac troponin T (cTnT) and BNP or NT-proBNP with intra-*participant* consistency.
16. Thyroid function panel includes: TSH; in case of abnormal TSH: fT3 (or T3, if fT3 is not available), and fT4. It will be performed during screening, every 3 months thereafter while participants are on treatment, at EOTV/EDV, and as clinically indicated.
17. Autoimmune panel includes: anti-nuclear antibodies (ANA) screen; only in case of a positive result in the ANA screen, anti-double-stranded DNA (dsDNA) antibodies, cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) need to be determined If one of these is positive, clinical work-up is needed to exclude any of the autoimmune diseases provided in the Exclusion Criteria.
18. Only to be performed if clinically indicated.
19. HIV, hepatitis B, and hepatitis C serology includes: anti-HIV-1 and anti-HIV2 (or anti-HIV-1/2), HBsAG, HBcAb, HBsAb, and anti-HCV.
20. *PCR testing for viral (HBV and HCV) load to be performed at Screening for all participants.* For participants with past or active HBV or past HCV infection fulfilling the criteria for study entry (see Section 5.1 *and Section 5.2),* PCR testing for viral load needs to be performed at Screening, on C2D1, C5D1, EOTV/EDV, and Safety F/U.
21. A serum pregnancy test will be performed at screening (within 7 days before the first study treatment administration on C1D1) and at the EOTV/EDV. In addition, a urine pregnancy test should be done every 3 weeks starting from C2D1, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
22. Radiological tumor assessments of chest, abdomen, and pelvis (CAP) for measuring extent of disease (CT scan is preferred method) will be done at screening, every 6 weeks following initiation of study treatment, and at EOTV/EDV. All known sites of disease documented at screening should be reassessed at each subsequent tumor evaluation. Results must be reviewed by the Investigator before dosing the next cycle. A ±7-days window is allowed for all tumor assessments. Comparison to baseline will be done by RECIST v1.1 and by iRECIST. In the absence of tumor progression, tumor assessments should continue regardless of whether participants discontinue study treatment, unless the participant starts subsequent anti-cancer treatment, dies, withdraws consent, or the study is terminated by the Sponsor, whichever occurs first.
23. *Step-up doses for RO7119929 under Schedule 2 are defined in Section 4.1.1.1.2. In case drug was not administered as planned during step-up dosing dose levels should not be skipped and continuation of step-up dosing should be agreed between the Investigator and the Medical Monitor.*

Table 1 Schedule of Activities for Part A and Part B (cont.)

24. RO7119929 will continue to be administered once weekly. If there is no visit scheduled, the drug will be administered by the participant at home.
25. *Tocilizumab pre-treatment for Schedule 3 is described in Section 4.1.1.1.3.*
26. Archival tumor tissue will be accepted from any time point prior to first dosing.
27. Only SAEs deemed related to RO7119929 by the Investigator are reportable outside the safety reporting period of 60 days after last study drug.
28. Every 3 months the sites will provide to the Sponsor with an update on survival status of each participant enrolled in the study. Post-study anti-cancer therapies should be collected and reported as appropriate in the eCRF.

Table 2 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for *Dose Escalation with Flat Dosing in* Part A *Schedules 1 and 3 (Without and With Tocilizumab Pre-treatment)*

Cycle (21 days)	Day	Scheduled time (h)	Time window	RO7119929 PK plasma	PD plasma (safety)	PD plasma	PD blood (RNA)	PD blood (DNA)	Blood (DNA)	RBR (DNA/ RNA	Tocilizu-mab PK serum[2]	Tocilizu-mab ADA[2]	Tocilizu-mab serum IL-6 PD markers[2]
Screening/ Baseline	D-28 to D-1												
Cycle 1	Day 1	Tocilizumab Predose	(within 24 hours prior to Tocilizu mab administr ation)								x	x	x
		RO7119929 Predose		x	x	x	x	x	x	x			
		0.25	± 5 min	x									
		0.5	± 5 min	x									
		1	± 10 min	x									
		1.5	± 15 min	x									
		2	± 15 min	x	x	x	x						
		3	± 15 min	x									
		4	± 15 min	x							x		x
		5	± 15 min	x									
		6	± 30 min	x	x	x	x						
		8	± 30 min	x									
		12	± 30 min	x	x	x	x						
	Day 2	24	± 2h	x	x	x	x				x		x
		30[1]	± 2h	x		x	x						
	Day 15[3]	RO7119929 Predose		x	x	x	x						
		2	± 15 min	x	x	x	x						
		8	± 30 min	x	x	x	x						

Table 2 Table 2 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for *Dose Escalation with Flat Dosing in* Part A *Schedules 1 and 3 (Without and With Tocilizumab Pre-treatment)* (cont.)

Cycle (21 days)	Day	Scheduled time (h)	Time window	RO7119929 PK plasma	PD plasma (safety)	PD plasma	PD blood (RNA)	PD blood (DNA)	Blood (DNA)	RBR (DNA/ RNA	Tocilizu-mab PK serum[2]	Tocilizu-mab ADA[2]	Tocilizu-mab serum IL-6 PD markers[2]
Cycle 2[4]	Day 1	RO7119929 Predose		x	x	x	x						
		0.25	± 5 min	x									
		0.5	± 5 min	x									
		1	± 10 min	x									
		1.5	± 15 min	x									
		2	± 15 min	x	x	x	x						
		3	± 15 min	x									
		4	± 15 min	x									
		5	± 15 min	x									
		6	± 30 min	x	x	x	x						
		8	± 30 min	x									
		12	± 30 min	x	x	x	x						
	Day 2	24	± 2h	x	x	x	x	x					
		30[1]	± 2h	x		x	x						
EOTV/EDV					x		x					x	
Unscheduled Visits[5]				x	x	x	x						

Table 2 Table 2 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for *Dose Escalation with Flat Dosing in* Part A *Schedules 1 and 3 (Without and With Tocilizumab Pre-treatment)* (cont.)

1. The 30 h time point for PK and PD sampling may be omitted in the course of the study subject to emerging PK data.
2. *Tocilizumab PK, ADA, and serum IL-6 PD (includes IL-6 and soluble IL-6R samples) to be taken only for Schedule 3 (with tocilizumab pre-treatment).*
3. *Based on review of emerging safety data with the single dose of tocilizumab pre-treatment, the Sponsor, in consultation with the investigators, may recommend an additional dose of tocilizumab be instituted prior to the C1D15 dose of RO7119929. In this case, tocilizumab PK, ADA, and serum IL-6 PD (includes IL-6 and soluble IL-6R) samples will need to be taken at tocilizumab predose (24 hours prior to the second tocilizumab administration) and tocilizumab PK and serum IL-6 PD samples after 6h (±30 minutes) and at Day 8 (±4 hours) after the second tocilizumab infusion.*
4. *In case no drug is administered on C2D1, all assessments planned for that day will be delayed to after the next drug administration.*
5. Unscheduled PK, PD plasma, PD plasma (safety)*, and PD blood (RNA)* samples will be taken at the time of development of any of the following events or at the earliest possible time thereafter: DLT event, dose reduction or treatment interruption due to AEs with CTCAE Grade ≥3 or CRS Grade ≥2 severity, clinically significant changes in ECGs, echocardiogram/MUGA or myocardial marker levels, such as troponin or pro-BNP levels, disease response (i.e., first time point of partial response or complete response), and disease progression. *If the EOTV/EDV coincides with an Unscheduled Visit as defined above, only the assessments for an Unscheduled Visit need to be performed.*

Table 3 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for *Dose Expansion With Flat Dosing in* Part B *Schedules 1 and 3 (Without and With Tocilizumab Pre-treatment)*

Cycle (21 days)	Day	Scheduled time (h)	Time window	RO7119929 PK plasma	PD plasma (safety)	PD plasma	PD blood (RNA)	PD whole blood (FACS)	Fresh tumor biopsy (mandatory)	PD blood (DNA)	Blood (DNA)	RBR (DNA/ RNA	Tocili-zumab PK serum[2]	Tocili-zumab ADA[2]	Tocilizu-mab serum IL-6 PD markers[2]
Screening/ Baseline	D-28 to D-1								x						
Cycle 1	Day 1	Tocilizumab Predose	(within 24 hours prior to Tocilizumab administration)										x	x	x
		RO7119929 Predose		x	x	x	x	x		x	x	x			
		0.25	± 5 min	x											
		0.5	± 5 min	x											
		1	± 10 min	x											
		1.5	± 15 min	x											
		2	± 15 min	x	x	x	x								
		3	± 15 min	x											
		4	± 15 min	x									x		x
		5	± 15 min	x											
		6	± 30 min	x	x	x	x								
		8	± 30 min	x											
		12	± 30 min	x	x	x	x								
	Day 2	24	± 2h	x	x	x	x						x		x
		30[1]	± 2h	x		x	x								

Table 3 Table 3 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for *Dose Expansion With Flat Dosing in* Part B *Schedules 1 and 3 (Without and With Tocilizumab Pre-treatment)* (cont.)

Cycle (21 days)	Day	Scheduled time (h)	Time window	RO7119929 PK plasma	PD plasma (safety)	PD plasma	PD blood (RNA)	PD whole blood (FACS)	Fresh tumor biopsy (mandatory)	PD blood (DNA)	Blood (DNA)	RBR (DNA/ RNA	Tocili-zumab PK serum 2	Tocili-zumab ADA2	Tocili-zu-mab serum IL-6 PD markers2
Cycle 1	Day 8	RO7119929 Predose						x							
	Day 15[3]	RO7119929 Predose		x	x	x	x	x							
		2	± 15 min	x	x	x	x								
		8	± 30min	x	x	x	x								
Cycle 2[4]	Day 1	RO7119929 Predose		x	x	x	x	x							
		0.25	± 5 min	x											
		0.5	± 5 min	x											
		1	± 10 min	x											
		1.5	± 15 min	x											
		2	± 15 min	x	x	x	x								
		3	± 15 min	x											
		4	± 15 min	x											
		5	± 15 min	x											
		6	± 30 min	x	x	x	x								
		8	± 30 min	x											
		12	± 30 min	x	x	x	x								
	Day 2	24	± 2h	x	x	x	x		x	x					
		30[1]	± 2h	x		x	x								
	Day 8	Predose						x							
	Day 15	Predose						x							
EOTV / EDV					x		x							x	
Unscheduled Visit[5]				x	x	x	x								

Table 3 Table 3 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for *Dose Expansion With Flat Dosing in* Part B *Schedules 1 and 3 (Without and With Tocilizumab Pre-treatment)* (cont.)

1. The 30 h time point for PK and PD sampling may be omitted in the course of the study subject to emerging PK data.
2. *Tocilizumab PK, ADA, and serum IL-6 PD (includes IL-6 and soluble IL-6R) samples to be taken only for Schedule 3 (with tocilizumab pre-treatment)*
3. *Based on review of emerging safety data with the single dose of tocilizumab pre-treatment, the Sponsor, in consultation with the investigators, may recommend an additional dose of tocilizumab be instituted prior to the C1 D15 dose of RO7119929. In this case, tocilizumab PK, ADA, and serum IL-6 PD (includes IL-6 and soluble IL-6R) samples will need to be taken at tocilizumab predose (24 hours prior to the second tocilizumab administration) and tocilizumab PK and serum IL-6 PD samples after 6h (± 30 minutes) and at Day 8 (± 4 hours) after the second tocilizumab infusion.*
4. Fresh biopsies are mandatory to be taken from the hepatic tumor lesion. In case no drug is administered on C2D1, the mandatory biopsy and all assessments planned for that day will be delayed to after the next drug administration.
   An additional (optional) biopsy at the time of disease progression, partial response, stable disease, or at any other time point of interest based on participant's course of disease may be taken after discussion between the Investigator and the Sponsor to aid the understanding of the resistance mechanisms.
5. Unscheduled PK, PD plasma, PD plasma (safety), *and PD blood (RNA)* samples will be taken at the time of development of any of the following events or at the earliest possible time thereafter: DLT event, dose reduction or treatment interruption due to AEs with CTCAE Grade ≥3 or CRS Grade ≥2 severity, clinically significant changes in ECGs, echocardiogram/MUGA or myocardial marker levels, such as troponin or pro-BNP levels, disease response (i.e., first time point of partial response or complete response), and disease progression. *If the EOTV/EDV coincides with an Unscheduled Visit as defined above, only the assessments for an Unscheduled Visit need to be performed.*

Table 4 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for Dose Escalation with Step-up Dosing in Part A Schedule 2

Cycle (21 days)	Day	Scheduled time (h)	Time window	PK plasma	PD plasma (safety)	PD plasma	PD blood (RNA)	PD blood (DNA)	Blood (DNA)	RBR (DNA/ RNA)
Screening/ Baseline	D-28 to D-1									
Cycle 1	Day 1	Predose		x	x	x	x	x	x	x
	Day 15	Predose		x	x	x	x			
		0.25	± 5 min	x						
		0.5	± 5 min	x						
		1	± 10 min	x						
		1.5	± 15 min	x						
		2	± 15 min	x	x	x	x			
		3	± 15 min	x						
		4	± 15 min	x						
		5	± 15 min	x						
		6	± 30 min	x	x	x	x			
		8	± 30 min	x						
		12	± 30 min	x	x	x	x			
	Day 16	24	± 2h	x	x	x	x			
		30[1]	± 2h	x		x	x			

Table 4 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for Dose Escalation with Step-up Dosing in Part A Schedule 2 (cont.)

Cycle (21 days)	Day	Scheduled time (h)	Time window	PK plasma	PD plasma (safety)	PD plasma	PD blood (RNA)	PD blood (DNA)	Blood (DNA)	RBR (DNA/ RNA)
Cycle 2[2]	Day 1	Predose		x	x	x	x			
		0.25	± 5 min	x						
		0.5	± 5 min	x						
		1	± 10 min	x						
		1.5	± 15 min	x						
		2	± 15 min	x	x	x	x			
		3	± 15 min	x						
		4	± 15 min	x						
		5	± 15 min	x						
		6	± 30 min	x	x	x	x			
		8	± 30 min	x						
		12	± 30 min	x	x	x	x			
	Day 2	24	± 2h	x	x	x	x	x		
		30[1]	± 2h	x		x	x			
	Day 15	Predose		x	x	x	x			
		2	± 15 min	x	x	x	x			
		8	± 30 min	x	x	x	x			
EOTV / EDV					x		x			
Unscheduled Visits[3]				x	x	x	x			

1. *The 30 h time point for PK and PD sampling may be omitted in the course of the study subject to emerging PK data.*
2. *In case no drug is administered on C2D1, all assessments planned for that day will be delayed to after the next drug administration*
3. *Unscheduled PK, PD plasma, PD plasma (safety), and PD blood (RNA) samples will be taken at the time of development of any of the following events or at the earliest possible time thereafter: DLT event, dose reduction or treatment interruption due to AEs with CTCAE Grade ≥3 or CRS Grade ≥2 severity, clinically significant changes in ECGs, echocardiogram/MUGA or myocardial marker levels, such as troponin or pro-BNP levels, disease response (i.e., first time point of partial response or complete response), and disease progression.*
   If the EOTV/EDV coincides with an Unscheduled Visit as defined above, only the assessments for an Unscheduled Visit need to be performed.

Table 5 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for Dose Expansion with Step-up Dosing in Part B Schedule 2

Cycle (21 days)	Day	Scheduled time (h)	Time window	PK plasma	PD plasma (safety)	PD plasma	PD blood (RNA)	PD whole blood (FACS)	Fresh tumor biopsy (mandatory)	PD blood (DNA)	Blood (DNA)	RBR (DNA /RNA)
Screening/ Baseline	D-28 to D-1								x			
Cycle 1	Day 1	Predose		x	x	x	x	x		x	x	x
	Day 8	Predose						x				
	Day 15	Predose		x	x	x	x	x				
		0.25	± 5 min	x								
		0.5	± 5 min	x								
		1	± 10 min	x								
		1.5	± 15 min	x								
		2	± 15 min	x	x	x	x					
		3	± 15 min	x								
		4	± 15 min	x								
		5	± 15 min	x								
		6	± 30 min	x	x	x	x					
		8	± 30 min	x								
		12	± 30 min	x	x	x	x					
	Day 16	24	± 2h	x	x	x	x					
		30[1]	± 2h	x		x	x					

Table 5 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for Dose Expansion with Step-up Dosing in Part B Schedule 2 (cont.)

Cycle (21 days)	Day	Scheduled time (h)	Time window	PK plasma	PD plasma (safety)	PD plasma	PD blood (RNA)	PD whole blood (FACS)	Fresh tumor biopsy (mandatory)	PD blood (DNA)	Blood (DNA)	RBR (DNA /RNA)
Cycle 2[2]	Day 1	Predose		x	x	x	x	x				
		0.25	± 5min	x								
		0.5	± 5min	x								
		1	± 10min	x								
		1.5	± 15min	x								
		2	± 15min	x	x	x	x					
		3	± 15min	x								
		4	± 15min	x								
		5	± 15min	x								
		6	± 30min	x	x	x	x					
		8	± 30min	x								
		12	± 30 min	x	x	x	x					
	Day 2	24	± 2h	x	x	x	x		x	x		
		30[1]	± 2h	x		x	x					
	Day 8	Predose						x				
	Day 15	Predose		x	x	x	x	x				
		2	± 15 min	x	x	x	x					
		8	± 30 min	x	x	x	x					
EOTV / EDV					x		x					
Unscheduled Visit[3]				x	x	x	x					

Table 5 Detailed Schedule of Activities for Pharmacokinetic and Pharmacodynamic Measurements for Dose Expansion with Step-up Dosing in Part B Schedule 2 (cont.)

1. *The 30 h time point for PK and PD sampling may be omitted in the course of the study subject to emerging PK data.*
2. *Fresh biopsies are mandatory to be taken from the hepatic tumor lesion. In case no drug is administered on C2D1, the mandatory biopsy and all assessments planned for that day will be delayed to after the next drug administration. An additional (optional) biopsy at the time of disease progression, partial response, stable disease, or at any other time point of interest based on participant's course of disease may be taken after discussion between the Investigator and the Sponsor to aid the understanding of the resistance mechanisms.*
3. *Unscheduled PK, PD plasma, PD plasma (safety), and PD blood (RNA) samples will be taken at the time of development of any of the following events or at the earliest possible time thereafter: DLT event, dose reduction or treatment interruption due to AEs with CTCAE Grade ≥3 or CRS Grade ≥2 severity, clinically significant changes in ECGs, echocardiogram/MUGA or myocardial marker levels, such as troponin or pro-BNP levels, disease response (i.e., first time point of partial response or complete response), and disease progression. If the EOTV/EDV coincides with an Unscheduled Visit, as defined above, only the assessments for an Unscheduled Visit need to be performed.*

2. INTRODUCTION

2.1 STUDY RATIONALE

The management of most advanced solid tumors remains challenging as only a small proportion of patients respond to standard of care therapy, and almost all patients progress on or after therapy. Cancer immunotherapy (CIT) with immune checkpoint inhibiting (CPI) monoclonal antibodies such as anti-programmed death-1 (PD-1)/anti-programmed death-ligand 1 (PD-L1), has changed the treatment landscape in many cancer types, however, a majority of patients with metastatic disease do not derive benefit from this type of CIT, particularly those with non-inflamed (immune deserted or immune excluded) tumors (Hedge et al 2016).

Toll-like receptor (TLR) 7 is a member of the TLR family, which encompasses a group of major regulators of the innate immune response (O'Neill et al 2013). TLR7 is an endosomal sensor of single-stranded RNA mainly expressed in hematopoietic cells, including plasmacytoid dendritic cells, macrophages, and B cells. TLR7 signals through MyD88, which results in a cytokine response (mainly IFN-α) and may promote an inflammatory microenvironment to foster effector T-cell activation and subsequent anti-tumor immunity. Multiple TLR7 agonists have entered clinical development for various tumor types. To date, their efficacy in early phase clinical studies has been hampered by several issues, including poor tolerability due to strong systemic cytokine activation (Dudek et al 2007, Chi et al 2017, Engel et al 2011).

RO7119929 is an orally administered prodrug of a TLR7 agonist. Conversion of RO7119929 to the active drug RO7117418 is mainly mediated through CYP2C9 and CYP2C19 metabolism. A predominantly hepatic activation is anticipated, based on the expression profile of these cytochromes as well as in vitro data generated in human hepatocytes and enterocytes demonstrating selective conversion in the liver. Together with a low solubility of the active drug RO7117418, this supports a rationale for evaluating tumors with predominant hepatic localization. The orally available prodrug approach may allow for an effective TLR7-mediated reprogramming of the immune microenvironment in the liver while limiting systemic immune effects.

WP41377 is a phase I study of RO7119929 given orally to participants with unresectable advanced or metastatic primary liver cancers (i.e., hepatocellular carcinoma [HCC], fibrolamellar HCC), intra-hepatic and perihilar biliary tract cancer (BTC) (i.e., intrahepatic cholangiocarcinoma [iCC], Klatskin tumor) and other solid tumors with predominant liver involvement. The primary objective of the study is to explore the safety and to determine the maximum tolerated dose (MTD) and/or optimal biologic dose (OBD) of RO7119929 as single agent.

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

2.2 BACKGROUND

RO7119929, an orally administered prodrug of a TLR7–specific agonist, is being developed for the treatment of patients with solid tumors, which have predominantly liver involvement.

A detailed description on the background of disease, current therapies, unmet medical needs as well as a description of the chemistry, pharmacology, and safety of RO7119929 is provided in the Investigator's Brochure.

2.3 BENEFIT/RISK ASSESSMENT

Clinical benefit from CIT with CPI monoclonal antibodies such as anti-PD-1/PD-L1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is predominantly observed in a subset of patients with immunogenic or inflamed tumors. In order to broaden the patient population that responds to immunotherapy, immune cell-activating compounds are required to generate a pro-inflammatory tumor micro-environment and sustain immune responses.

TLR7 agonists have been tested in various preclinical and clinical investigations. They stimulate innate immune cells leading to the activation of humoral and cellular immunity, thus engendering a series of anti-tumor activities (Chi et al 2017). Imiquimod (Aldara®), a TLR7 agonist, was approved by the FDA for the topical treatment of skin cancers. However, when given systemically, TLR7 agonists have shown only modest clinical activity, mainly due to systemic immune activation leading to dose limiting toxicities (Dudek et al 2007, Gadd et al 2015, Engel et al 2011).

RO7119929 is a pro-drug that is converted to the active drug RO7117418 primarily in the liver. RO7117418 stimulates TLR7 positive cells within the liver and tumor, resulting in a cytokine response and promoting an inflammatory microenvironment to foster effector T-cell activation and subsequent anti-tumor immunity. In preclinical models, the TLR7 agonist demonstrated strong pharmacodynamic (PD) effects consistent with the postulated mode of action (MoA) and exerted anti-tumor activity as single agent and particularly in combination with a CPI.

Due to the pro-drug design, RO7119929 is hypothesized to achieve high levels of inflammation at the site of liver tumors, while effectively limiting systemic immune activation.

Potential and identified risks for RO7119929 are detailed in the Investigator's Brochure. These potential *and identified* risks have been taken into account in the safety measures for this study, which include the definition of strict eligibility criteria (Section 5), *dose-limiting toxicities (*DLTs*;* Section 8.3.7), rules for treatment interruption and withdrawal from study (Section 7), and recommendations for the prophylaxis and the management of specific adverse events (AE; Section 8.3.8).

For participants in Part B of the study, the collection of mandatory baseline and on-treatment tumor samples from hepatic lesions will permit an assessment of the PD effects of RO7119929. In order to mitigate the potential risk associated with this procedure, all participants must have – according to inclusion criteria for Part B – tumor manifestations from which biopsies can safely be obtained. In order to reduce the risk of bleeding, adequate coagulation is required for entry into the study (see Section 5.1).

After the biopsies are taken, participants will be monitored adequately to further mitigate the risk of unobserved bleeding.

In conclusion, the TLR7 agonist RO7119929 presents an opportunity to boost the immune response in patients with primary and secondary liver cancers in an effort to contribute to better clinical outcomes. The non-clinical *and clinical* data sets for RO7119929 in conjunction with the planned safety monitoring and management guidance provide an acceptable risk-benefit balance for the clinical investigation of RO7119929 in advanced cancer patients for whom no effective standard therapy exists.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected adverse events of RO7119929 is provided in the Investigator's Brochure.

COVID-19 Benefit/Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities (including those with liver cancer) are a more vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses (Liang et al 2020, Guan et al 2020). It is unclear how immunotherapy affects the incidence or severity of COVID-19. It is not anticipated that treatment with RO7119929 will increase the risk of infection with SARS-CoV-2. Severe COVID-19 is associated with cytokine release syndrome (CRS) involving the inflammatory cytokines IL-6, IL-10, IL-2, and interferon-gamma (Merad and Martin 2020). Based on the anticipated mode of action of RO7119929, there may be a potential for an enhanced inflammatory response including CRS if a participant experiences SARS-CoV-2 infection while receiving RO7119929. Study WP413377 is currently ongoing during this pandemic and, although the number of enrolled participants is small, no increased risk of developing COVID-19 has been observed.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in *Table 6*.

Table 6 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate safety and tolerability of RO7119929 (prodrug) in participants with solid tumors with predominant liver involvement *with and without tocilizumab pre-treatment* • To determine the maximum tolerated dose (MTD) and/or optimal biologic dose (OBD)	• Nature and frequency of dose-limiting toxicities • Incidence, nature and severity of adverse event according to NCI CTCAE v5.0

Objectives	Endpoints
for RO7119929 *with and without tocilizumab pre-treatment*	
Secondary	
• To evaluate the PK profile of RO7119929 and RO7117418 (active drug) following oral administration of RO7119929 in participants with solid tumors with predominant liver involvement • To evaluate the effect of food on pharmacokinetics of RO7119929 and RO7117418 after administration of RO7119929 in participants with solid tumors with predominant liver involvement	• PK parameters such as C_{max}, T_{max}, AUC, $T_{1/2}$ for RO7119929 and RO7117418 following administration of RO7119929 • Effect of a meal on PK parameters such as C_{max}, T_{max}, AUC, $T_{1/2}$ for RO7119929 and RO7117418 following administration of RO7119929 compared to fasting conditions
• To evaluate peripheral blood for biomarkers to support optimal biological dose and schedule selection	• Change in inflammatory PD biomarkers in peripheral blood such as IFN-α and ISGs
• To assess preliminary clinical activity of RO7119929 administration in participants with solid tumors with predominant liver involvement	• Objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DOR) • Progression-free survival All of the above will be evaluated according to RECIST v1.1. • Overall survival
• To assess preliminary clinical activity signals of RO7119929 administration in participants with solid tumors with predominant liver involvement with respect to liver lesions only	• ORR • DCR • DOR All of the above will be evaluated according to RECIST v1.1 with respect to responses in liver lesions only.
Exploratory	
• To explore the relationship between PK and PD *for RO7119929 with and without tocilizumab pre-treatment* • To explore the effect of polymorphisms and gender on PK, PD, and safety of RO7119929 and RO7117418	• Dependence of PD assessments in peripheral blood such as *safety cytokines (e.g., IL-6, TNF-a),* IFN-α*,* and ISGs on exposure to RO7117418 • Dependence of PK and PD endpoints on polymorphisms (such as CYP2C9,

Objectives	Endpoints
• To explore the effect of hepatic function on PK, PD, and safety of RO7119929 and RO7117418	CYP2C19, UGT1A9, UGT1A1, and TLR7) and gender • Dependence of PK and PD endpoints on hepatic function
• To evaluate biomarkers in peripheral blood and tumor tissue for response *and safety* prediction	• Biomarker assessments in peripheral blood such as *protein and* RNA-based analysis • Biomarker assessments in archival and/or fresh pretreatment tumor tissue such as gene/protein expression of TLR7 and PD-L1, CYP genotype, and viral status (HBV and HCV)
• To evaluate biomarkers in peripheral blood and tissue from paired tumor biopsies to demonstrate proof of mechanism	• Biomarker assessments in peripheral blood such as activation of immune cell subsets • Biomarker assessments in paired tumor biopsies such as re-programming of the TME and T-cell infiltration and activation
• To investigate the presence of RO7119929-derived metabolite(s) in plasma • To assess relative abundance and PK parameters of any metabolite as appropriate	• PK parameters of circulating RO7119929-derived metabolite(s)
• To assess preliminary clinical activity of RO7119929 administration in participants with solid tumors with predominant liver involvement	• ORR • DCR • DOR • Progression-free survival All of the above will be evaluated according to immune RECIST (iRECIST).
• To assess preliminary clinical activity signals of RO7119929 administration in participants with solid tumors with predominant liver involvement with respect to liver lesions only	• ORR • DCR • DOR All of the above will be evaluated according to iRECIST with respect to responses in liver lesions only.

Objectives	Endpoints
• To assess preliminary clinical activity of RO7119929 administration on extra-hepatic tumor manifestations in participants with measurable extra-hepatic disease	• ORR according to RECIST v1.1 and according to iRECIST with respect to extra-hepatic tumor manifestations only.

Abbreviations: DCR=Disease control rate; DOR=Duration of response; HBV=hepatitis B virus; HCV=hepatitis C virus; OBD=Optimal biologic dose; ORR=Objective response rate; PD=Pharmacodynamics; PK=Pharmacokinetics.

4. STUDY DESIGN

4.1 OVERALL DESIGN

4.1.1 Study Overview

WP41377 is a first in human, open label, multi-center, multiple-ascending dose escalation, Phase I study consisting of two parts: Part A (dose escalation) and Part B (dose expansion). *In addition, the effect of food intake on the pharmacokinetics (PK) of RO7119929 will be investigated.*

RO7119929 will be administered weekly (QW) in 3-week cycles. Within Part A, three different schedules will be investigated: Schedule 1 (QW flat dosing), Schedule 2 (QW step-up dosing), and Schedule 3 (QW flat dosing with tocilizumab pre-treatment). Other treatment schedules may be explored, based on emerging data after amending the protocol accordingly. *Part B may enroll up to three expansion cohorts at different doses and/or dosing schedules based on emerging clinical and PD data.*

If dose escalation cohorts (Part A) and dose expansion cohorts (Part B) are open in parallel, the Sponsor will decide where to enroll each participant. Depending on evolving data, these decisions might aim at enrichment of certain participant subgroups within the PD expansion cohorts, e.g., by selection for certain tumor types.

If two or more dose expansion cohorts are open in parallel, enrollment into these cohorts will be decided by randomization.

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

4.1.1.1 Study Part A (Dose Escalation)

Part A of this study will define the MTD/RDE *for different dosing schedules (see Section 4.1.1.1.1, Section 4.1.1.1.2, and Section 4.1.1.1.3)* by escalating doses of RO7119929 as a single agent in adult patients with advanced or metastatic solid tumors with predominant liver involvement. Participants will be enrolled in cohorts with at least 3 evaluable participants, treated in a staggered manner (at least 1 week between the first and second participant and at least 24 hours between subsequent participants).

Treatment will consist of a screening period (Day -28 to Day -1), a treatment period (Cycle 1 Day 1 to month 12; the length of the study may be modified based on emerging data), a time period following treatment discontinuation (concluded by an end of treatment visit [EOTV] within 28 days of last study drug, followed by a safety follow-up visit 60 days after last study drug), and post-treatment survival follow-up assessments every 3 months for up to 24 months. Safety assessments for DLT determination will be

performed during the first 3 weeks (21 days) *or 4 weeks (28 days), depending on schedule.* Drug administration during the treatment period will continue until disease progression, unacceptable toxicities, or withdrawal of the participant's consent up to a maximum of 12 months or 17 cycles, whichever comes first. As with other immunotherapies, treatment beyond progressive disease according to the response evaluation criteria in solid tumors (RECIST v1.1) can be considered, if deemed in the best interest of the study participant (see Section 7.1).

Dose escalation will be carried out according to a modified continual reassessment method (mCRM) with overdose control (mCRM-EWOC design). Dose escalation decisions and selection of the dose for the next cohort will be subject to clinical judgement by the Sponsor and the participating Investigators following review of all safety and available PK and/or PD data and not based solely on DLT information, while guided by the CRM-EWOC recommendation.

For exploring the effect of food intake on the PK of RO7119929 *in Part A, participants* will receive RO7119929 after a defined meal (see Section 5.3.1) at *the time of first target dose (*Cycle 1 Day 1 *or Cycle 1 Day 15, depending on schedule)* and following a 10-hour fast at Cycle 2 Day 1 enabling intra-participant comparison. For this pilot food effect (FE) study, a minimum of 6 evaluable participants will be enrolled across several cohorts.

Participants who experience DLTs may be considered for continued study treatment at a reduced dose, following regression of toxicity to ≤ Grade 1 and a discussion with and agreement of the Sponsor (see Section 6.6).

Any of the Part A*-schedules* may be paused or halted prior to identification of MTD and upon sufficient characterization of the IMP in regards to safety, PK and/or PD.

4.1.1.1.1 Schedule 1 (Flat Dosing on a QW Schedule)

Within Schedule 1, RO7119929 will be administered QW at the same dose in 3-week cycles. During dose escalation, the dose will be determined using an mCRM-EWOC design (see Appendix 6). The DLT period will consist of the first 3 weeks (21 days), corresponding to the first cycle.

The starting dose for the dose escalation will be 1 mg (see Section 4.3)

4.1.1.1.2 Schedule 2 (Step-up Dosing on a QW Schedule)

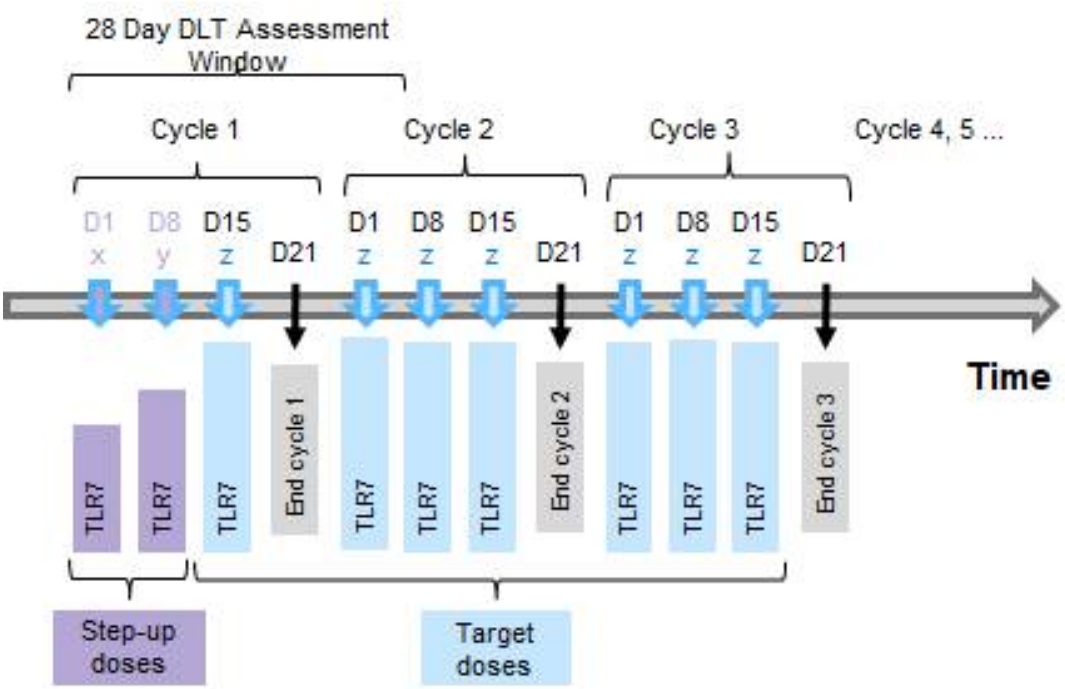
Within Schedule 2, RO7119929 will be administered QW in 3-week cycles with step-up dosing during Cycle 1 (see Figure 2). The dosing step at Cycle 1 Day 1 will be fixed at a dose level with minimal risk of CRS Grade ≥2, while the dosing step at Cycle 1 Day 8 will be fixed at a dose with an acceptable dose-toxicity profile guided by safety information in the flat dosing cohorts (Schedule 1).

The target dose at Cycle 1 Day 15 will be determined using an mCRM-EWOC design (see Appendix 6). The target dose will then be administered QW during each subsequent cycle. The DLT period will consist of the first 4 weeks (28 days).

The starting dose at Cycle 1 Day 15 for Cohort 1 of the dose escalation will be identical to the dose administered at Cycle 1 Day 8.

For more information, see Section 4.2.5.

Figure 2 Dosing Schedule for Step-up Dosing



D=Day; DLT=Dose-limiting toxicity; TLR7= RO7119929; x,y,z=doses of increasing strength.

4.1.1.1.3 Schedule 3 (Flat dosing on a QW Schedule with Tocilizumab Pre-treatment)

Within Schedule 3, RO7119929 will be administered QW at the same dose in 3-week cycles. Tocilizumab will be administered as pre-treatment on Cycle 1 Day 1, approximately 2 hours prior to RO7119929 administration. The benefit of a second dose of tocilizumab on Cycle 1 Day 15 may be tested after agreement between the Sponsor and Investigators, if a significant number of participants had no signs of CRS or CRS Grade 1 at Cycle 1 Day 1 and/or Cycle 1 Day 8 but still experienced CRS ≥2 at Cycle 1 Day 15 and/or Cycle 2 Day 1 during dose escalation. If successful, this regimen will be used in future cohorts.

The DLT period will consist of the first 3 weeks (21 days) and will be prolonged to the first 4 weeks (28 days) in case of implementation of a second tocilizumab administration at Cycle 1 Day 15.

During dose escalation, the dose of RO7119929 will be determined using an mCRM-EWOC design (Appendix 6). The starting dose for the dose escalation will be 4 mg, a dose with an acceptable dose-toxicity profile in the flat dosing cohorts (Schedule 1).

For more information, see Section 4.2.5.

4.1.1.2 Study Part B (Dose Expansion)

Following determination of MTD and/or RDE, treatment will commence at up to three different doses *and/or dosing schedules (Section 4.1.1.1.1, Section 4.1.1.1.2, and*

Section 4.1.1.1.3) in specific expansion cohorts of participants for extended PD analysis, including collection of peripheral blood and mandatory paired tumor biopsies taken from the hepatic tumor manifestations to demonstrate proof of mechanism (PoM).

Each expansion cohort will enroll approximately 10 PD-evaluable participants. Participants with both available and evaluable tumor biopsy samples will be considered evaluable for the PD endpoint. If signs of relevant anti-tumor and/or PD activity are observed within Part A at dose levels below MTD, it may be decided to initiate Part B at this dose level *and schedule (i.e., 1, 2, or 3)* before Part A is complete after discussion and alignment between the Investigators and the Sponsor.

Treatment for all participants in Part B will consist of a screening period (Day -28 to Day -1), a treatment period (Cycle 1 Day 1 to month 12), a treatment discontinuation period (within 28 days of last study drug until EOTV), one safety follow-up visit and post-treatment survival follow-up assessments. Drug administration during the treatment period will continue until disease progression, unacceptable toxicities, or withdrawal of the participant's consent up to a maximum of 12 months. As with other immunotherapies, treatment beyond progressive disease according to RECIST v1.1 can be considered, if deemed in the best interest of the study participant (see Section 7.1).

The effect of food intake on PK data may be explored within Part B if less than 6 evaluable participants were included *in* Part A *(see Section 4.1.1.1 and Section 5.3.1)*.

4.1.2 Length of the Study

See "End of study definition" in Section 4.4.

4.1.3 Dose Escalation Decision Criteria

4.1.3.1 Dose Escalation in Part A

Dose escalation of RO7119929 will start with a dose of 1 mg in at least 3 DLT-evaluable participants. The potential dose grid for dose administrations is from 1 mg to 10 mg by 1 mg, from 10 mg to 20 mg by 2 mg, from 20 mg to 50 mg by 5 mg, from 50 mg to 150 mg by 10 mg, and from 150 mg to 250 mg by 25 mg.

The decision to escalate to the next dose level is made when at least 3 participants in a cohort have completed the DLT period (21 days *or 28 days, respectively, Section 4.1.1.1.1, Section 4.1.1.1.2, and Section 4.1.1.1.3*), based on the review of all relevant safety information collected, including AEs, ECGs, vital signs, and clinical laboratory test results. In addition, available PK and PD data at the current and/or previous dose level(s) will be reviewed.

At each dose escalation step, the dose can be escalated or de-escalated and/or an additional cohort at that same dose level could be enrolled. The next dose level will be recommended by the EWOC design during the dose escalation phase and discussed and agreed by the Sponsor, the Investigators and any other person that the Investigator considers necessary to assist with the decision. The Sponsor and Investigators will be able to overrule the EWOC design recommendation based on the data available.

Built-in safety constraints are in place to prevent exposing participants to undue risk of toxicity, i.e., the maximum allowable dose-increment in absence of DLT will be 200% from 1 mg to 10 mg, 100% from above 10 mg to 60 mg, and 50% above 60 mg. Independent of these rules, if one DLT occurs, the increment is restricted to a maximum of 100% for all future dose steps.

The maximum dose that will be explored is 250 mg, and the maximum *allowable* sample size is 60 participants for Part A, based on trial simulations using several hypothetical dose-toxicity profiles.

Details of the dose escalation design including operating characteristics based on the trial simulations can be found in Appendix 6.

4.1.3.2 Dose Limiting Toxicity (DLT) Observation Period and DLT Criteria

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) or significant laboratory abnormality 1) occurring during an assessment period of 21 *days or 28* days after first dose of study treatment, *respectively*, and 2) is not attributed to disease progression, concomitant illness or another clearly identifiable cause.

Adverse events considered DLTs are listed in *Table 7*.

The following are not considered DLTs:

- Toxicities fulfilling the DLT definition that occur outside of the DLT period will be considered for the determination of the overall tolerability and safety profile of RO7119929.
- Alopecia (any Grade).
- Grade 3 nausea, vomiting or diarrhea, including their clinical sequelae (e.g. fluid loss with subsequent dehydration, electrolyte loss occurring with sub-optimal prophylactic and curative treatment and that are responding to supportive care within 72 hours).
- Grade ≥3 fatigue that resolves to Grade ≤2 within 7 days.
- Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤2 within 7 days.
- Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with the exception of cases suspicious of drug-induced liver injury as defined in Appendix 3, Section 6:
    - Treatment-emergent ALT or AST >3 x baseline value in combination with total bilirubin ≥2 x ULN (of which ≥35% is direct bilirubin).

- Treatment-emergent ALT or AST >3 x baseline value in combination with clinical jaundice.

- Grade ≥3 laboratory abnormality that is asymptomatic and deemed by the Investigator not to be clinically significant.

During Part A dose escalation, participants who withdraw before the end of the DLT period for reasons other than DLTs will be replaced to ensure that all participants in each cohort have been assessed for the full DLT period prior to moving to the next dose level.

Table 7 Adverse Events Considered Dose-limiting Toxicities

SOC Disorder	NCI CTCAE Term	DLT Criteria
Blood and lymphatic system disorders	Neutropenia (neutrophil count decreased)	Grade 4 neutropenia (<0.5G/l) lasting ≥5 consecutive days
	Febrile neutropenia	Grade ≥3 neutropenia (<1.0G/l) associated with single body temperature ≥38.3°C or sustained body temperature ≥38°C for ≥1 hour, and/or with infection
	Lymphopenia	Grade ≥3 CD4 lymphocytes decreased (<0.2G/l) or grade ≥3 lymphocyte count decreased (0.5 G/l) lasting ≥5 consecutive days
	Anemia	Grade 4 anemia or Grade ≥3 anemia with hemolysis
	Thrombocytopenia (platelet count decreased)	Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with clinically significant bleeding and/or bleeding episodes requiring a platelet transfusion
	Activated partial thromboplastin time prolonged	Grade ≥3
		Any other grade ≥3 blood and lymphatic system disorder that is not listed among the exceptions in Section 4.1.3.2.
Non-hematologic disorders	Cytokine release syndrome	Grade ≥3 (hypotension managed with ≥1 vasopressor or hypoxia requiring ≥40% O_2)
		Any other grade ≥3 non-hematological toxicity that is not listed among the exceptions in Section 4.1.3.2.

Abbreviations: DLT=Dose-limiting toxicity; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; SOC=System organ class.

4.1.4 Stopping Rules Criteria

During *each schedule within* the dose escalation in Part A, the model will recommend to stop if:

- At least 12 participants have been evaluated and at least 6 participants have been observed at a dose close to MTD (i.e., a dose differs by at most 10%) and the posterior probability that (0.2 ≤Prob[DLT | dose] ≤0.35) for the next best dose is above 50% OR
- The maximum of 60 DLT-evaluable participants is reached OR
- A minimum of 6 participants has been accrued at the maximum dose or near (differing from the maximum dose by at most 10%) and it is at least 50% likely that the probability of a DLT for that maximum dose is below 20%

In addition, the dose escalation could be halted upon sufficient characterization of RO7119929 in regards to safety and PK and without MTD determination.

In Part B, cohorts may be stopped for unacceptable toxicity. The criteria for unacceptable toxicity are detailed in Section 8.3.7.

Expansion cohorts may be stopped also if a strategic decision is made by the Sponsor to stop further development of RO7122290.

4.1.5 Communication Strategy

Information will be communicated as follows:

- Upon completion of all screening evaluations and confirmation that a participant has met all inclusion and exclusion criteria, sites will contact the Sponsor to confirm the participant number and cohort assignment via a Confirmation of Enrollment form. This will guarantee that the Sponsor is notified prior to the administration of RO7119929.
- For all participants, during dose escalation in Part A, the Investigator(s) must confirm to Roche that the participant has been dosed and provide a brief summary of the status of the participant in terms of safety and tolerability to RO7119929, communicated by email and/or telephone.
- In the event of a DLT, the Investigator will contact the Sponsor immediately to discuss participant status and action taken/to be taken.
- During dose escalation in Part A, after completion of each participant cohort (i.e., minimum of 3 DLT-evaluable participants; after the last participant in the cohort has reached the last day of the DLT period without the observation of a DLT) the Sponsor will organize a teleconference with the Investigators to discuss the safety and tolerability of RO7119929 and to discuss the dose(s) for the next cohort. If the teleconference occurs prior to the end of the DLT evaluation period, the Investigator will provide a final status prior to start of the next cohort.

- During each teleconference:
    - NCI-CTCAE (v5.0) toxicities (see Appendix 2) will be discussed along with the results of PK data (if available), in addition to safety laboratory results and any other available data that may assist the dose escalation decision process.
    - Dose escalation decisions and selection of the dose for the next cohort of participants will be made following review of all relevant available data, as well as the EWOC recommendations. Dose escalation will only proceed to the next dose level if the Investigators and the Sponsor are satisfied with the safety profile of the previous cohort and agree to move to the next dose level.
    - The discussion will be documented in writing, 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, as per normal interactions during the conduct of a clinical study, and the Sponsor will arrange regular teleconferences and meetings to discuss 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.

4.1.6 Administrative Structure

The Sponsor is responsible for the study management (monitoring), data management, statistical analysis, and medical writing of the Clinical Study Report. A Clinical Study Report will be written and distributed to Health Authorities, as required by applicable regulatory requirements. The protocol will be submitted to country/institutional Ethics Committees. For further details, see Appendix 1.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Study WP41377 is a first-in-human, open-label, multicenter Phase I dose escalation study of single agent RO7119929 consisting of two parts (see overall study design Section 4.1).

The dose escalation part (Part A) of this study will *explore three different schedules and* use a Bayesian model-based approach (for statistical rationale see Section 4.2.5). The primary objective of Part A is to determine an MTD or RDE *for each of the schedules*.

Part B consists of up to three specific expansion cohorts at different dose levels *and/or dosing schedules* for extended PD analysis including collection of peripheral blood and mandatory paired tumor biopsies to demonstrate PoM (for details on biomarker assessment rationale see Section 4.2.2). As the PD effect may not be strictly dose-dependent once a pharmacologically active dose is reached, different doses *may*

be tested for both proximal and distal PD effects in order to determine the OBD. The dose cohorts for Part B may be selected after completion of Part A and following analysis of all relevant safety information, PK data, and peripheral blood biomarkers. However, if signs of relevant anti-tumor and/or PD activity are observed during Part A at dose levels below MTD, it may be decided to start the first expansion cohort before Part A is complete after discussion and alignment between the Investigators and the Sponsor.

The study rationale is provided in Section 2.1.

4.2.1 Rationale for Study Population

This study will enroll participants with advanced or metastatic primary hepatic tumors (HCC, BTC) or with metastasized extra-hepatic solid tumors with predominant liver involvement and for whom no effective standard therapy exists. The selection of tumors with predominantly hepatic localization is due to the prodrug design of the study drug, which results in predominant hepatic conversion to the active drug and thus an intra-hepatic induction and priming of the anti-tumor response. However, due to the expected systemic proliferation of activated tumor-specific T cells, an anti-tumor effect in extra-hepatic tumor manifestations may also be observed.

Depending on evolving data, the Sponsor may aim to enrich certain participant subgroups within the PD expansion cohorts, e.g., by selection for certain tumor types.

4.2.2 Rationale for Biomarker Assessments

RO7119929 was designed to target and activate TLR7 positive immune cells. As a biologic consequence of TLR7 engagement, cells are activated and mature. This results in an increase of T-cell priming activities of e.g. TLR7+ APCs and release of pro-immunostimulatory cytokines and chemokines to enable and facilitate anti-tumor immunity.

Non-clinical studies have demonstrated a dose-dependent increase of IFN-stimulated genes downstream of TLR7 signaling such as ISG15 or OAS1 as well as the induction of pro-inflammatory cytokine such as IFN-α, IL-6, IL-8, CCL2, TNFα, and IL-2 (for details see Investigator's Brochure). Further, these studies confirmed the hypothesized mode of action of RO7119929 by showing an activation of TLR7 positive immune cells such as dendritic cells, monocytes/macrophages, and B cells as well as NK cells. Hence, PD markers downstream of TLR7 signaling will be assessed from peripheral blood pre-dose and on-treatment for all dose levels *and schedules*. Based on non-clinical data, the dose-dependent induction of IFN-α and ISG 15 will be prioritized (see *Section 1.3* and Section 8.7).

In addition, to monitor PD cytokine release in the context of safety, plasma/serum analysis for selected cytokines/chemokines such as IL-6, IL-8, IP-10, TNFα, and sCD25 will be monitored in parallel with PD dose selection markers.

Beyond TLR7 *expression*, drug converting CYP2C9, CYP2C19 as well as drug transporters and metabolizing enzymes such as UGT1A9 and UGT1A1 gene polymorphisms and their respective ethnic prevalence can impact the direct TLR7 dependent activation pathway or the (pro)-drug conversion rate and the active drug clearance. To characterize the SNPs prevalence versus the observed PK/PD relationship, a genetic DNA based analysis will be performed from a pre-treatment blood sample for all participants treated with RO7119929 (see *Section 1.3* and Section 8.7).

For Part B, the biomarker endpoint is to demonstrate proof of mechanism by investigating distal PD markers (i.e. the biological consequence of TLR7 activation) in the tumor. Therefore, Part B represents up to 3 dedicated PoM cohorts tested at defined dose levels with mandatory paired pre- and post-treatment tumor biopsies in primary liver cancer (HCC, BTC) or metastatic disease to the liver. Biopsies have to be taken from the hepatic lesion and will be used to analyze changes of cytokine/chemokine gene expression in the tumor microenvironment (TME; Table 3, *Table 5*, and Section 8.7, fresh mandatory biopsy). In addition, a direct link between reprogramming of the tumor microenvironment and activation of TLR7+ immune cells in the TME will be investigated.

Secondary effects of TLR7 stimulation on T cells induced by single agent RO7119929 will be characterized in Part B in blood and tumor tissue. The activation and spatial location of tumor infiltrating T lymphocytes will be monitored from the paired tumor tissue biopsies (Table 3 *and Table 5*; fresh mandatory tumor biopsies) as well as the activation of peripheral T cells in the blood. Additional tumor markers such as PD-L1 and fibroblast activation protein (FAP) expression in tumor tissue may be investigated in the context of potential combination partners (see Section 8.7).

As potential additional surrogate markers for tissue based tumor-infiltrating lymphocyte (TIL) activation, 2 additional peripheral blood samples will be collected to investigate the RO7119929 mediated changes to the peripheral TCR Vβ repertoire as indicated by external non-clinical and clinical studies (Diab et al 2019). The analysis of potential TCR Vβ repertoire changes, however, may be gated to successful demonstration of PoM (*Section 1.3* and Section 8.7).

All specimens for the described and additional exploratory biomarker assessments will be used for research purposes to support the optimal dose/schedule selection of RO7119929, to monitor safety, to demonstrate PoM, and to identify response prediction/ mechanism of resistance to therapy.

4.2.3 Rationale for Pharmacokinetic Assessment

In this study, RO7119929 will be tested in humans for the first time. Therefore, it is important to fully characterize the PK profile of RO7119929 and its metabolite, RO7117418, the active drug of RO7119929 *at different schedules with and without tocilizumab pre-treatment.* Serial PK samples (i.e., multiple time points of collection post oral administration) will be performed per the SoA (see *Section 1.3*). Due to uncertainty in

the human PK prediction and an observed prolonged flat-terminal phase after IV administration of RO7117418 in the monkey, an additional 30 h time point for PK and PD sampling will be taken in the first cohorts in Part A. The 30 h sampling may be omitted during the course of the study in case this prolonged flat-terminal phase is not observed in humans.

- Additionally, the effect of food intake on the PK of RO7119929 will be explored. RO7119929 is a biopharmaceutics classification system (BCS) class 1 drug with a high first-pass metabolism and the PK can be affected by meals. This food effect pilot study during dose escalation in Phase I aims to show that food does not have a clinically significant impact on the PK of RO7119929 and that future clinical trials can be conducted without regard to food.

To understand the relationship between RO7119929 and RO7117418 plasma exposure and efficacy/safety, unscheduled PK samples will be taken at the time of development of any of the following events, or at the earliest possible time thereafter:

- DLT event
- Dose reduction or treatment interruption due to AEs with CTCAE Grade ≥3 or cytokine release syndrome (CRS) Grade ≥2 severity
- Clinically significant changes in ECGs, echocardiogram/MUGA or myocardial marker levels, such as troponin or pro-BNP levels, disease response (i.e., first time point of complete response or partial response), disease progression
- Disease response (i.e., first time point of complete response [CR] or partial response [PR])
- Disease progression

4.2.4 Rationale for the Treatment of Cytokine Release Syndrome Using Tocilizumab

CRS is a potentially life-threatening symptom complex, caused by the excessive release of cytokines by immune effector or target cells during an exaggerated and sustained immune response. CRS can be triggered by a variety of factors, including infection with virulent pathogens, or by medications that activate or enhance the immune response, resulting in a pronounced and sustained immune response.

Regardless of the inciting agent, severe or life-threatening CRS is a medical emergency. If unsuccessfully managed, it can result in significant disability or fatal outcome. Current clinical management focuses on treating the individual signs and symptoms, providing supportive care, and attempting to dampen down the inflammatory response using high dose corticosteroids. However, this approach is not always successful, especially in the case of late intervention.

CRS is associated with elevations in a wide array of cytokines, including marked elevations in IFN-γ, IL-6, and TNF-α levels. Emerging evidence implicates IL-6 as a

central mediator in CRS. IL-6 is a pro-inflammatory multi-functional cytokine produced by a variety of cell types, which has been shown to be involved in a diverse array of physiological processes including T-cell activation. CRS is associated with high IL-6 levels (Panelli et al 2004, Lee et al 2014, Doessegger and Banholzer 2015), and IL-6 correlates with the severity of CRS with patients who experience severe or life-threatening CRS (CTCAE Grades 3 or 4), having much higher IL-6 levels compared to their counterparts who do not experience CRS or only experience milder CRS reactions (CTCAE Grades 0 to 2) (Chen et al 2016).

Tocilizumab (Actemra®/RoActemra®) is a recombinant, humanized, anti-human monoclonal antibody directed against soluble and membrane-bound IL-6R, which inhibits IL-6 mediated signaling. Blocking the inflammatory action of IL-6 using tocilizumab could therefore represent a novel approach for the treatment of CRS. Refer to the *tocilizumab* Investigator's Brochure for further details.

CRS is associated with T-cell recruiting therapies including CAR-T-cell therapy and bispecific molecules such as blinatumomab. There have been multiple reports in the literature of tocilizumab being used off-label to successfully treat severe or life-threatening CRS with different underlying causality (Teachey et al 2013, Lee et al 2014, National Institute of Health 2017, Frey and Porter 2019, Ascierto et al 2020), and tocilizumab is now approved in the U.S. for the treatment of CAR T-cell-induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older.

In addition, recent literature supports the use of tocilizumab for management of moderate cases of CRS (Neelapu et al 2018, Riegler et al 2019).

Transient elevations of IL-6 have been observed in patients experiencing CRS Grade ≥2 following the administration of RO7119929, including high levels of IL-6 (see the RO7119929 Investigator's Brochure for details).

Together, these findings indicate that patients treated with RO7119929 who develop *CRS Grade ≥2* may benefit from tocilizumab therapy*; nevertheless, tocilizumab* should be used only after careful consideration of the benefit/risk in a given participant. Section 8.3.9 *provides* recommendations regarding the management of CRS.

4.2.5 *Rationale for RO7119929 Step-up Dosing (Schedule 2)*

Step-up dosing has repeatedly shown to be an effective measure to improve the safety profile in cancer immunotherapies associated with CRS, in particular in the context of T-cell bispecific antibodies. For instance, blinatumomab has been demonstrated to be tolerated at its recommended Phase II dose only in the context of Cycle 1 step-up dosing (Blincyto USPI; Viardot et al 2016).

CRS has been identified as a risk for RO7119929, particularly in Cycle 1. The transient cytokine release observed after dosing of RO7119929 is similar to the cytokine profile described for T-cell bispecific antibodies including blinatumomab. After a fast and strong increase of cytokine levels

such as IFN-α, IL-6, TNF-α, and IP10 during Cycle 1 Day 1, a trend for lower peak concentrations is seen at Cycle 2 Day 1, indicating a potential tolerance effect. This observation is in line with the reduced manifestation of CRS frequency and severity in Cycle 2 compared to Cycle 1 (RO7119929 Investigator's Brochure).

The dose escalation administering a flat dose of RO7119929 (Schedule 1) is ongoing and the MTD and OBD have not yet been established. A two-step dose escalation (Schedule 2) is being added to this study to assess the safety, tolerability, and pharmacokinetics of a two-step dosing regimen in Cycle 1.

4.2.6 *Rationale for Using Tocilizumab for Pre-treatment (Schedule 3)*

Initial clinical data (Locke et al 2017) suggest tocilizumab prophylaxis may reduce the severity of CAR-T cell-induced CRS by blocking IL-6 receptors from signaling prior to cytokine release. While emerging clinical data suggest that earlier intervention with tocilizumab may mitigate CRS induced by bispecific antibodies (Kauer et al 2020), to date, no clinical data on tocilizumab pre-treatment for prevention of CRS induced by any cancer immunotherapy besides CAR-T cells have been published.

Highly elevated levels of IL-6 have been reported to be immunosuppressive, impairing IFN-γ production and CD8 T cell function (Velazquez-Salinas et al 2019, Wu et al 2015). Specifically in cancer immunotherapy, elevated IL-6 levels lead to reduced immune-mediated tumor-cell killing (Tsukamoto et al 2018, Liu et al 2017). It is therefore hypothesized that blockage of excess IL-6 signaling may prevent CRS while possibly enhancing anti-tumor activity of RO7119929.

Schedule 3 will thus evaluate the efficacy of tocilizumab as pre-treatment in ameliorating the frequency and/or severity of CRS in the first cycle following treatment with RO7119929. The tocilizumab dose to be tested as pre-treatment will be 8 mg/kg for participants ≥ 30 kg in weight (dose not to exceed 800 mg) and 12 mg/kg for participants < 30 kg in weight. This is based on the currently approved IV dose of tocilizumab for the treatment of CRS and is consistent with the Sponsor's CRS management guidelines (Table 9). Up to three additional doses may be given, at 8-hour intervals, to treat CRS if CRS develops after administration of RO7119929 despite pre-medication (Section 8.3.9). The administration of tocilizumab pre-medication will be 2 hours prior to RO7119929 dosing to ensure both sufficient time to complete the tocilizumab infusion and close proximity to RO7119929 administration.

Schedule 3 will first test a single dose of tocilizumab (prior to the Cycle 1 Day 1 dose of RO7119929). Based on the review of emerging safety data with the single dose of tocilizumab pre-treatment, the Sponsor, in consultation with the investigators, may recommend an additional dose of tocilizumab be instituted prior to Cycle 1 Day 15 dose of RO7119929 (Section 4.1.1.1.3).

4.2.7 Rationale for the Statistical Design

The dose escalation Part A of this study will use a Bayesian model-based approach, i.e., the mCRM-EWOC design (Neuenschwander et al 2008). The use of Bayesian model-based phase I designs has been advocated by Rogatko (Rogatko et al 2007) and is one of the key elements of the FDA's Critical Path Initiative. Clinical judgment can always override the Bayesian adaptive design recommendations in the dose-selection process. The primary objective of a dose escalation study (including the present study) is to determine an MTD or recommend the dose for expansion. DLTs are the driver of dose allocation and act as an important factor to define the MTD. DLTs traditionally are defined by the occurrence of severe toxicities during a relatively short period of systemic cancer therapy, which is called the DLT observation window.

Toxicity induced by RO7119929 in the pre-clinical studies occurred predominantly early after the initial administration of the drug. Therefore, in line with this, DLTs will be evaluated during *the first 21* to *28* days*, depending on schedule (Section 4.1.1.1)*.

The mCRM-EWOC design has many favorable characteristics: First, it adaptively fits a DLT-dose-response curve by incorporating toxicity data from eligible participants among different cohorts, and non-clinical or clinical information from compounds with similar MoA contributes by building an informative prior distribution of the statistical model. Second, it locates the MTD accurately without pre-specifying dose levels in each cohort. Dose-selections are made based on the DLT-dose-response curve measured by a two parameter logistic model over the dose range, subject to clinical judgment and mandated safety constraints that limit the size of dose increments. Moreover, the EWOC algorithm highly reduces risks of exposing participants to overly toxic doses. Such model-based designs have been successfully applied in many Phase I dose escalation studies (Schöffski et al 2004, Le Tourneau et al 2009, and Neuenschwander et al 2008). In addition, hypothetical dose escalation runs using the design and simulations demonstrate the validity of the operating parameters of the design as implemented for this study (Appendix 6).

4.3 JUSTIFICATION FOR DOSE

A starting dose of 1 mg has been selected for this first-in-human study. This dose is based on the no-observed-adverse-effect level (NOAEL) in cynomolgus monkeys, the most relevant animal species. The 1 mg dose is derived from exposure-based conversion of GLP monkey NOAEL data under the low clearance and volume of distribution under steady-state conditions (V_{ss}) assumption (most conservative estimation) in human, applying a standard safety factor of 10. Based on PK and PD modeling, this dose is expected to be safe and associated with little or no measurable PD effect, and lower than the estimated pharmacologically active dose (3 to 30 mg, considering the uncertainty in human clearance and V_{ss}).

The safety margins associated with the starting dose have been based on the preclinical toxicokinetic data and the estimated NOAEL in the toxicology studies performed.

For the starting doses for step-up dosing (Schedule 2) and flat dosing with tocilizumab pre-treatment (Schedule 3), refer to Section 4.1.1.1.2 and Section 4.1.1.1.3.

Further details are provided in the Investigator's Brochure.

4.4 END OF STUDY DEFINITION

The end of this study is defined as the date when the last participant, last visit occurs or after approximately 14 months (screening phase 28 days, treatment period up to 12 months, and follow-up period 28 days) after the last participant is enrolled, whichever occurs first. For an individual participant, the completion of the study (i.e., the last visit) will occur when the participant withdraws consent, has been lost to follow-up, dies, or when the study is stopped. Because of the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor.

5. STUDY POPULATION

This study will enroll adults with unresectable advanced or metastatic HCC, BTC, or specific solid tumors with predominant liver involvement (see below).

The study population rationale is provided in Section 4.2.1.

5.1 INCLUSION CRITERIA

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

- Signed written informed consent and the ability to comply with the study protocol according to the International Council for Harmonisation (ICH) and local regulations.
- Age ≥18 years.
- Histologically confirmed diagnosis of one of the following:
    - Participants with unresectable advanced or metastatic HCC (including fibrolamellar HCC) not amenable to a curative treatment approach. For participants with cirrhosis, clinical diagnosis by the American Association for the Study of Liver Diseases (AASLD) criteria is sufficient (Appendix 10).
    - Participants with unresectable advanced or metastatic intrahepatic or perihilar (Klatskin) BTC not amenable to a curative treatment approach.
    - Participants with extrahepatic BTC or gallbladder cancer infiltrating the liver or metastasized into the liver with predominant liver disease, not amenable to a curative treatment approach.
    - Participants with metastasized colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), gastric cancer (GC), renal cell carcinoma

(RCC), triple-negative breast cancer (TNBC), cutaneous melanoma, or ocular melanoma with predominant liver disease not amenable to a curative treatment approach. Participants with other solid tumors with predominant liver disease not amenable to a curative treatment approach might be enrolled after Sponsor approval.

- Measurable disease with at least one measurable locally untreated liver lesion, as defined by RECIST v1.1.
    - Participants who received prior local therapy to the liver (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) are eligible provided the target lesion(s) have not been previously treated with local therapy or the target lesion(s) within the field of local therapy have subsequently progressed in accordance with RECIST v1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Adequate hematologic function, defined by laboratory assessment documented within 7 days prior to Cycle 1 Day 1 treatment:
    - Absolute neutrophil count (ANC) ≥1500/μL, white blood cell (WBC) ≥2500/μL without granulocyte colony-stimulating factor support
    - Hemoglobin ≥9.0 g/dL
    - Platelet count ≥75,000/μL without transfusion
- Adequate major organ functions, defined as:
    - Serum creatinine ≤1.3 × upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/min/1.73 m2 using the Modification of Diet in Renal Disease Study (MDRD) formula
    - Serum bilirubin ≤2 × ULN
    - Serum transaminases ≤3 × ULN
    - Serum alkaline phosphatase ≤5 × ULN
    - Serum albumin ≥ 2.8 g/dL without transfusion
    - For participants not receiving therapeutic anticoagulation: International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤2 × ULN
- Documented virology status of hepatitis, as confirmed by screening *hepatitis B virus (*HBV*), hepatitis C virus (*HCV*)* serology*, and viral load* test.
- Participants for which there is no available standard therapy likely to confer clinical benefit, or participants who are not candidates for such available therapy.

- Life expectancy of ≥12 weeks, approximated with Royal Marsden Hospital score 0-1 (Arkenau et al 2009) or Gustave Roussy Immune (GRIm) score 0-1 (Bigot et al 2017). See scores in Appendix 14. Participants with a Royal Marsden Hospital or GRIm score of ≥2 and a life expectancy of ≥12 weeks according to the investigator's clinical judgement may be enrolled after Medical Monitor approval has been obtained.
- For participants with HCC: Child-Pugh score of *A6* or better (Appendix 11).
- 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, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.
- 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 conditions apply:
    - Woman of non-child bearing potential (WONCBP) as defined in Appendix 5.
    - Woman of childbearing potential (WOCBP), who:
        - Agrees to remain abstinent (refrain from heterosexual intercourse) or use two highly effective contraceptive methods that result in a failure rate of <1% per year, during the treatment period and for at least one month after the last dose of study drug RO7119929 and 3 months after the last dose of tocilizumab, whichever is longer. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs (see Appendix 5). Hormonal contraceptive methods must be supplemented by a barrier method.
        - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
        - Has a negative pregnancy test (blood) within seven days prior to the first study drug administration.
- Male participants: During the treatment period and for at least 30 days after the final dose of treatment RO7119929 and at least 60 days after the last dose tocilizumab, agreement to:

- With a partner who is a WOCBP (as defined in Appendix 5), 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 a pregnant female partner, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing embryo.
- Refrain from donating sperm for at least 30 days after the final dose of RO7119929 and 60 days if tocilizumab treatment.

Additional Inclusion Criteria for Study Part B:

- Ability to obtain and consent for tumor biopsy specimen collection at pre-study baseline and one additional post-treatment biopsy sample collected during treatment on Cycle 2 Day 2, each from a liver lesion.

  Of note, a lesion considered for biopsy should not be selected as target lesion. Therefore, eligible patients need to present with at least two liver lesions, of which at least one needs to be measurable, as defined by RECIST v1.1. Patients with only one measurable liver lesion, as defined by RECIST v1.1, may be considered after consultation with the Sponsor.

5.2 EXCLUSION CRITERIA

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

- History or clinical evidence of central nervous system (CNS) primary tumors or metastases including leptomeningeal metastases, unless they have been previously treated, are asymptomatic, and have had no requirement for steroids or enzyme-inducing anticonvulsants in the last 14 days prior to Screening.
- Evidence of any extra-hepatic primary tumor or metastasis requiring prompt medical intervention.
- Receipt of prior therapy with a TLR7/8/9 agonist and/or IFN-α.
- Prior chemotherapy, antibody, or other registered or experimental cancer treatment within 3 weeks of study Cycle 1 Day 1. Specifically, no CPI antibody is allowed to be administered within 6 weeks of study Cycle 1 Day 1.
- Receipt of investigational agent for any other indication within 3 weeks of dosing.
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant

medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.

  - Patients who received mineralocorticoids (e.g., fludrocortisone), for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
  - Patients who are tapered off systemic corticosteroids as part of a prior cancer regimen must have received the last dose ≥7 days prior to initiation of study treatment.

- Radiotherapy or *major* surgery within 3 weeks of dosing. Palliative radiotherapy to bone lesions is allowed. Patients should be recovered from the effects of radiation *and/or surgery*.
- Local therapy to liver (e.g. radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, and transarterial embolization) within 3 weeks prior to initiation of study treatment, radioembolization within 3 months prior to initiation of study treatment, or non-recovery from side effects of such procedure.
- Treatment-related toxicities from prior cancer therapy that have not resolved to ≤ Grade 1 CTC AE prior to study treatment with the exception of the following Grade 2 toxicities: alopecia, peripheral neuropathy, any laboratory changes that still lie within the inclusion criteria defined above.
- History of other malignancy within 2 years; exception for ductal carcinoma in situ not requiring chemotherapy, low grade cervical intraepithelial neoplasia (CIN), non-melanoma skin cancer, low grade localized prostate cancer (Gleason score < Grade 7), or optimally treated Stage 1 uterine cancer.
- Active or history of immunologic-mediated disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjogren's syndrome or Guillain-Barré syndrome (for a more comprehensive list of autoimmune diseases and immune deficiencies see Appendix 12), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study.
  - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of the 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.
- Positive laboratory result for anti-mitochondrial, anti-smooth muscle, or thyroid peroxidase antibodies, unless further work-up has been performed to exclude autoimmune liver diseases (such as primary biliary cirrhosis and autoimmune hepatitis) and autoimmune thyroiditis.
- 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). This includes Epstein-Barr virus (EBV) or other acute active viral infection including *Varicella* zoster virus (VZV) and cytomegalovirus (CMV).
- Severe infection within 4 weeks prior to initiation of study treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment.

  Please note: Patients receiving prophylactic antibiotics (e.g. to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior allogenic stem cell or solid organ transplantation.
- History of human immunodeficiency virus (HIV) infection
- *A*ctive hepatitis B virus infection

  Note: Patients with active HBV can be enrolled if

    - HBV DNA <500 IU/mL obtained within 28 days prior to initiation of study treatment AND
    - Anti-HBV treatment (per local standard of care) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study.
- *Coinfection of HBV and HCV*
  Note: Active hepatitis C infection is defined as having a positive HCV RNA test at screening. Patients with a history of HCV infection who are negative for HCV-RNA by PCR will be considered non-infected with HCV.
- History of clinically significant cardiovascular, endocrine, pulmonary, gastrointestinal, or psychiatric disorder as follows:

- Hypertensive crisis/encephalopathy, uncontrolled hypertension (systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg; average of ≥3 readings in ≥2 sessions), stroke, acute coronary syndrome, congestive heart failure according to New York Heart Association (NYHA) >1 or left ventricular ejection fraction (LVEF) <50%, serious cardiac arrhythmia that requires treatment with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia within 6 months of enrolment.
- History of pulmonary embolism within 3 months of enrolment.
- Non-controlled diabetes (HbA1c >7%) or diabetic retinopathy.
- History of pulmonary disorders including interstitial pneumonitis, bronchiolitis obliterans, pulmonary hypertension, and sarcoidosis.
- History of chronic pancreatitis or acute pancreatitis within the last 6 months of enrolment.
- History of major depression with suicidal ideation within the last 5 years.

- Ascites, pleural effusion, or pericardial effusion requiring medical intervention (including use of diuretics) within 12 months prior to study entry.
- For patients with HCC:
  - Untreated or incompletely treated esophageal and/or gastric varices with history of bleeding or high risk for bleeding
- Note: Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone an EGD within 6 months prior to initiation of study treatment do not need to repeat the procedure.
  - History of hepatic encephalopathy
  - History of main portal vein thrombosis or evidence of hepatofugal portal venous flow
- Active alcohol or substance abuse as documented by the Investigator.
- *Vaccination with a live or live-attenuated vaccine within 28 days prior to Day 1.*
- A clinically significant concomitant disease or condition that could interfere with the conduct of the study protocol or that would pose an unacceptable risk for the participant in the opinion of the Investigator.

5.3 LIFESTYLE CONSIDERATIONS

There are data suggesting that milk thistle products (Silybum marianum; Flavonolignans silybin) may inhibit CYP2C9 and UGT1A1 (Grimstein et al 2018). Therefore, participants should minimize the amount of milk thistle supplementation from Day -1 until the end of treatment period.

5.3.1 Meals and Dietary Restrictions

No specific food is prohibited in this study.

The effect of food intake on the PK of RO7119929 will be explored in a minimum of 6 evaluable participants across several Part A cohorts. The participants will receive doses of RO7119929 while fed at Cycle 1 Day 1 *(Schedules 1 and 3, flat dosing) or at Cycle 1 Day 15 (Schedule 2, step-up dosing)* and while fasted at Cycle 2 Day 1 enabling intra-participant cross-over comparison. The dose cohorts in which the food effect will be studied will be selected based on emerging PK and PD data (above the predicted minimal pharmacologically active dose).

Following an overnight fast of at least 10 hours, RO7119929 will be administered after a standard meal (i.e. 400-1000 calories, 25-50% fat; meal should be eaten in 30 minutes or less) at Cycle 1 Day 1 *or Cycle 1 Day 15, respectively,* and in fasted condition at Cycle 2 Day 1. In both cases, RO7119929 should be taken together with 240 mL of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after drug administration. In both cases, food should not be consumed for at least 4 hours after the dose. The food intake during the standard meal will be recorded on the *electronic Case Report Form (eCRF).*

For dosing events that are not part of the food effect evaluation, RO7119929 will be given in fasted state (at least 2 hours after a meal or 2 hours before the next meal).

Alcohol consumption is to be strongly discouraged. During the study, participants should consume no more than an average of 20 g of alcohol per day. Participants will be queried on a regular basis about their alcohol consumption and appropriate comments concerning this intake will be recorded on the *eCRF.*

5.4 SCREEN FAILURES

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

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once, with Sponsor approval. In the event re-screening is permitted, invasive assessments like biopsies do not have to be repeated if agreed by the Medical Monitor. 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).

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.

For the purpose of the study, only RO7119929 and tocilizumab are considered investigational medicinal products (IMP). All IMPs required for completion of this study will be provided by the Sponsor. Study drug administration will take place both at the study center under supervision of qualified site staff and at the participant's discretion.

6.1 TREATMENTS ADMINISTERED

The administered treatments are summarized in Table 8.

Table 8 Summary of Treatments Administered

Study Treatment Name:	RO7119929	Tocilizumab[1]
IMP and NIMP	IMP	IMP
Dose Formulation:	Capsule	Concentrate for solution for IV infusion
Unit Dose Strength(s)/Dosage Level(s):	1 mg, 5 mg, 25 mg	200 mg/10 mL
Dose:	Part A starting dose will be 1 mg	*For participants ≥* 30 kg: 8 mg/kg *IV* For participants < 30 kg: 12 mg/kg IV
Route of Administration:	Oral	IV infusion
Dosing Regimen:	Every week (QW)	NA
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling:	Study treatment will be provided in HDPE bottles. Each HDPE bottle will be labeled as required per country requirement.	Tocilizumab will be provided in a carton box (one labeled vial per box). Each carton box will be labeled as required per country requirement.

HDPE=high-density polyethylene; IMP=investigational medicinal product; IV=intravenous; NA=not applicable; NIMP=non-investigational medicinal product; QW=every week.

1 In an emergency situation, tocilizumab may be obtained locally by the study sites *(where approved by local health authorities)* and will be formulated, prepared, and handled according to standard practice. Refer to the local prescribing information for further instructions regarding recommended storage conditions and packaging configuration.

6.1.1 RO7119929

RO7119929 will be administered as described in the Pharmacy Manual. Guidelines for dosage modification are provided in Section 6.6 and guidelines for treatment interruption or discontinuation are provided in Section 7.

6.1.2 Tocilizumab *Pre-Treatment*

In this study tocilizumab will be administered as pre-treatment in Schedule 3 (Section 1.3). In addition, it can be used to manage CRS associated with RO7119929 in all study schedules.

The efficacy of tocilizumab in the management of a potential CRS associated with RO7119929 is unknown. Hence, tocilizumab should be used *for treatment of CRS* only after careful consideration of the benefit/risk in a given participant. Section 8.3.9 provides recommendations for the management of CRS. The SoA for tocilizumab treatment *to manage CRS* can be found in Appendix 13.

Tocilizumab will be provided by the Sponsor. In an emergency situation where the study-specific labeled supply of tocilizumab is not accessible, it may be supplied locally by the study sites (where approved by local health authorities) and will be formulated, prepared, and handled according to the local prescribing information. The study-specific labeled supply of tocilizumab should always be used for pre-treatment in Schedule 3.

Tocilizumab will be administered at room temperature by controlled IV infusion over a 1-hour period. The infusion rate must be 10 mL/hr for 15 minutes and then increased to 130 mL/hr to complete the dosing over the 1-hour time period. Normal saline (20 mL) will be administered following infusion of study drug to flush the remaining study drug through the IV set.

For more details, see the tocilizumab Investigator's Brochure and Pharmacy Manual.

6.1.3 Pre-medication for RO7119929

All pre-medications should be captured on a dedicated pre-medications page in the participant's eCRF.

At Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15, the participant should be pre-medicated with 500 mL of crystalloid fluid and 500-1000 mg paracetamol PO or IV at the time of RO7119929 administration (±30 minutes), followed by 500-1000 mg paracetamol PO or IV 4-6 hours after first drug administration. If no CRS is observed, no further pre-medication is foreseen beyond Cycle 1. If a participant develops CRS despite pre-medication, procedures for management of CRS will be initiated as described in Section 8.3.9.

If Grade ≥2 CRS is seen in a significant proportion of participants during dose escalation (Part A), the benefit of prophylactic pre-medication with corticosteroids (e.g., 10-20 mg dexamethasone or equivalent) may be tested in Cycle 1 after agreement between the Sponsor and Investigators. If successful, this regimen will be used in future cohorts.

Pre-medication for participants who experience a Grade ≥2 CRS is to be administered for the subsequent dose according to the AE management guidelines in Section 8.3.9.

The pre-medication regimens are based on the expected duration of inflammatory events and may be modified based on emerging data.

Pre-treatment with tocilizumab in Schedule 3 is described in Section 6.1.2.

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

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

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

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

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

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, Institution, or the Head of the Medical Institution (where applicable) 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 or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the Pharmacy Manual and/or the RO7119929 Investigator's Brochure and the tocilizumab Investigator's Brochure for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

All participants must provide written informed consent before any study-specific assessments or procedures are performed. Sites will be required to notify the Sponsor of planned participant screening in order to manage recruitment. An Eligibility Checklist documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed and signed by the Investigator (or designee). The Eligibility Checklist will also capture the allocated screening number for the participant. When the clinical significance of an abnormal screening test result (laboratory or any other test) is considered uncertain, the test will be repeated.

If dose escalation *cohorts (*Part A*)* and *dose* expansion *cohorts (*Part B*)* are open in parallel, the Sponsor will decide where to enroll each participant. Depending on evolving data, these decisions might aim to enrich certain participant subgroups within the PD expansion cohort, e.g., by selection for certain tumor types.

If two or more expansion cohorts at different dose levels are open in parallel, enrollment into these cohorts will be determined by randomization.

6.3.2 Blinding

This is an open-label study, blinding is not applicable.

6.4 TREATMENT COMPLIANCE

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

From Cycle 5 onward, if no site visit is scheduled and drug administration is not performed by site personnel, participants will use a medication diary to record taking the study drug at home.

6.5 CONCOMITANT THERAPY

6.5.1 Rescue Medicine

Not applicable.

6.5.2 Permitted Therapy

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

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

All concomitant medications should be reported to the Investigator and recorded on the concomitant medications eCRF.

All medication administered to manage adverse events should be recorded on the Adverse Event eCRF and any non-pharmacological interventions (e.g., individual psychotherapy, cognitive behavioral therapy, or rehabilitative therapy) should be recorded as appropriate on the eCRF.

Systemic corticosteroids and immune suppressants may attenuate potential beneficial immunologic effects of treatment. If deemed necessary for the treatment of immune-related toxicities, systemic corticosteroids may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered.

Limited field palliative radiotherapy or elective surgery during the course of the clinical study can be permitted after discussion with and agreement of the Sponsor. No delay of study treatment administration is foreseen, although participants should not receive radiation or surgery at a day of study treatment.

6.5.3 Prohibited Therapy

RO7119929 might inhibit CYP3A in the gastro-intestinal tract during its absorption. Co-medications known to be moderate and strong CYP3A substrates should be therefore administered at least 4 hours before and 2 hours after RO7119929 to minimize the risk of increased exposure of these co-medications. For example, administer RO7119929 in the morning of dosing and the co-medications at lunchtime for that day only. Thereafter, co-medications can be taken as normal. For the list of co-medications known to be moderate and strong CYP3A substrates, refer to Appendix 7.

Conversion of RO7119929 to the active drug RO7117418 is mainly mediated through CYP2C9 and CYP2C19 metabolism in the liver. Co-medications known to interfere with CYP2C9 and CYP2C19 by moderate and strong inhibition are generally prohibited as they might inhibit the conversion of RO7119929 during first pass but might be allowed after discussion with the Sponsor. For a list of co-medications known to be moderate and strong CYP2C9 and CYP2C19 inhibitors refer to Appendix 7.

The active drug RO7117418 is an OATP1B1 substrate and inhibitor (IC50 = 1.3 μM). Co-medication that is known to inhibit OATP1B1/1B3 might increase the exposure to the active drug RO7117418 and should therefore be administered at least 4 hours before and 8 hours after RO7119929. With weekly dosing and the predicted short half-life, no substantial effect is expected for co-medications known to be substrates of OATP; however cautionary on days when RO7119929 is administered, co-medications known to be OATP substrates should be administered at least 4 hours before and 8 hours after RO7119929. For example, administer RO7119929 in the morning of dosing and the co-medications in the afternoon for that day only. Thereafter, co-medications can be taken as normal. For a list of co-medications known to be OATP substrates and inhibitors refer to Appendix 7.

The active drug RO7117418 is mainly metabolized by UGT1A9 and to a lesser extent by UGT1A1 and UGT1A3. Co-medication known to be UGT1A9 and UGT1A1/1A3 inhibitors might increase the exposure of the active drug RO7117418 and should therefore be administered at least 4 hours before and 8 hours after RO7119929. For example, administer RO7119929 in the morning of dosing and the co-medications in the afternoon for that day only. Thereafter, co-medications can be taken as normal. For a list of co-medications known to be UGT1A9 and UGT1A1/1A3 inhibitors refer to Appendix 7.

All preventive and routine immunizations (e.g., tetanus/diphtheria booster, herpes zoster, pneumococcal pneumonia, or influenza) should preferentially be administered at least 28 days prior to initiation of study treatment. If an immunization is needed during the study, it should not be administered during the DLT assessment period in the dose escalation Part A, prior to completion of Cycle 2 Day 2 in the dose expansion Part B, or immediately following resolution of a CRS event of Grade ≥2. The timing of the vaccination should allow recovery of all AEs from previous study drug administration and should not lead to a dose delay, allowing for the resolution of vaccine related events. Vaccination with a live or live-attenuated vaccine is not permitted within 28 days prior to initiation of study treatment and during study treatment.

The use of the following therapies is prohibited during the study and for at least 21 days prior to initiation of study treatment, unless otherwise specified:

- Investigational or unlicensed/unapproved agents
- Immunotherapy/radio-immunotherapy
- Chemotherapy

- Immuno-stimulatory agents
- Radiotherapy (with the exception of limited field palliative radiotherapy)
- Biologic agents
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. Systemic corticosteroids, TNF-α inhibitors, mycophenolate, and other immune suppressants may be administered for the treatment of immune-related toxicities at the discretion of the treating physician after consultation with the Medical Monitor.

6.6 DOSE MODIFICATION

No intra-participant dose escalations will be permitted before the first tumor assessment on treatment as indicated in the SoA. Intra-participant dose escalations after the first tumor assessment will be permitted at the discretion of the Investigator and in agreement with the Sponsor. Participants may receive a dose of RO7119929 that is at least one dose level below the highest currently evaluated dose in *the dose escalation with the same schedule*, if that dose has been considered safe. Dose escalations will only be allowed to occur at the beginning of a treatment cycle.

During the DLT assessment period of the dose escalation schedules (Part A) participants who experience toxicities fulfilling the definition of a DLT (see definition in Section 4.1.3.2) *may be considered for continued study treatment at a reduced dose, following regression of toxicity to Grade ≤1 if deemed in the best interest of the participant by the Investigator and agreed* with the Sponsor.

In Part A, and Part B, after the occurrence of a toxicity that requires withholding of study treatment, participants may restart RO7119929 therapy at the cohort-identified dose once the toxicity resolves to Grade ≤ 1 or baseline. For details regarding management of specific AEs and treatment re-initiation, see Section 8.3.9, Table 9.

After discussion with the Sponsor, RO7119929 treatment may also be resumed at a lower dose if the participant is deriving clinical benefit and *a* toxicity is judged to be significant in the opinion of the Investigator whereby the Investigator does not wish to dose at the same dosing level. In case a dose reduction is necessary, the study treatment will be administered at a dose level that is between 30% and 80% of the current dose taken by the participant and has been considered safe. No intra-participant dose re-escalations are allowed, and the dose may not be reduced more than three times for a participant. For temporary dose interruptions, see Section 7.1.1.

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide RO7119929 or other study interventions to participants after conclusion of the study or any earlier participant withdrawal.

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

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

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

7.1 DISCONTINUATION OF STUDY TREATMENT

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

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

- Participant withdrawal of consent at any time.
- DLT as defined in Section *4.1.3.2*.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study.
- Disease progression when there is a consensus between the Investigator and the Sponsor that the participant will not benefit from study treatment.
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant.
- Pregnancy.
- Any event that meets stopping criteria defined in Section *4.1.4*.

As with other immunotherapies, treatment beyond RECIST v1.1 progression may be considered following discussion between the Investigator and the Sponsor. The criteria below are needed for continuing treatment beyond initial apparent progressive disease per RECIST v1.1:

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

Every effort should be made to obtain information on participants who withdraw from the study treatment but have not withdrawn consent. Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.11.3) and may undergo follow-up assessments (see Section 8.11.4), unless the participant withdrew consent. The primary reason for

premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely may be replaced at discretion of the Sponsor.

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 restart as soon as medically justified in the opinion of the Investigator. For additional information on dose modifications, see Section 6.6. Restart of study treatment after a dose interruption of more than 3 weeks may be allowed, if the participant is benefitting from study treatment per Investigator and after consultation with the Sponsor.

If RO7119929 administration is delayed by more than 2 days from the schedule administration date, the dose will then be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose of RO7119929 will not be made up.

Within Schedule 2 or Schedule 3, a participant may be required to repeat step-up dosing or tocilizumab pre-treatment following a dose interruption. If a participant missed one or more doses of RO7119929 within Schedule 2 or Schedule 3, the Investigator should consult with the Medical Monitor to determine if repeat step-up dosing or repeat tocilizumab pre-treatment is required. The Sponsor may also request the participant to repeat Cycle 1 assessments including local and central laboratory assessments.

7.1.2 Resumption of Study Treatment

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

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

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

Participants who withdraw from the study for safety reasons will not be replaced. Participants who withdraw from the study for other reasons after the end of the DLT period will not be replaced.

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

If treatment is discontinued and consent has not been withdrawn, the participant will still be followed for survival endpoints.

Participants will be treated until progressive disease, unacceptable toxicities or withdrawal of consent up to a maximum of 12 months. This period can be prolonged if the participant derives a clinical benefit from the treatment after discussion with the Medical Monitor and approval by the Sponsor.

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.

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time-points are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Any 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 was performed within the time-frame defined in the SoA.

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

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

Vital sign monitoring will be implemented for the different study schedules as follows:

After the first administration of RO7119929 *at Cycle 1 Day 1 for flat dosing without (Schedule 1) or with (Schedule 3) tocilizumab pre-treatment*, the participant will be hospitalized and observed by regular vital sign monitoring for at least 24 hours (at least every hour for the first 8 hours, then every 4 hours, and as clinically indicated). If the first dosing *with RO7119929* is tolerated without AEs, further administrations of the drug will be monitored as follows:

- Subsequent 3 doses (up to C*ycle* 2 D*ay* 1): 8 hours of hourly vital sign monitoring

  Note: In case of a second dose of tocilizumab pre-treatment provided on Cycle 1 Day 15 (Schedule 3), 8 hours of hourly vital sign monitoring is also required at Cycle 2 Day 8.

- Subsequent 8 doses (up to Cycle 4 Day 15): 2 hours of hourly vital sign monitoring
- All subsequent doses: no vital sign monitoring

After the first two administrations of RO7119929 at Cycle 1 Day 8 and Day 15 for step-up dosing (Schedule 2), 8 hours of hourly vital sign monitoring are required. After administration of RO7119929 at the target dose at Cycle 1 Day 15, the participant will be hospitalized and observed by regular vital sign monitoring for at least 24 hours (at least every hour for the first 8 hours, then every 4 hours, and as clinically indicated). If the first target dosing with RO7119929 is tolerated without AEs, further administrations of the drug will be monitored as follows:

- *Subsequent dose (Cycle 2 Day 1) and Cycle 2 Day 15: 8 hours of hourly vital sign monitoring*
- *Cycle 2 Day 8 and Cycle 3 Day 1 to Cycle 4 Day 15: 2 hours of hourly vital sign monitoring*
- *All subsequent doses: no vital sign monitoring*

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Tumor assessments will be performed at the time-points defined in the SoA (Section 1.3). All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be performed according to the RECIST v1.1, and at least one hepatic target lesion needs to be defined (see Appendix 8).

The extent of neoplastic disease will be determined by reproducible radiographic techniques, preferably computed tomography (CT) or magnetic resonance imaging (MRI) scan. Ultrasound and X-rays are not acceptable for monitoring target lesions.

Computed Tomography or MRI scans should include chest, abdomen, and pelvic scans, with additional examinations performed if clinically indicated (e.g., bone scans and CT scans of the neck).

All known and suspected areas of neoplastic disease will be evaluated. For each participant, the same method of assessment and the same technique must be used consistently throughout the entire study. Use of spiral CT or MRI is required for screening lesions < 20 mm and must be documented in medical records and used consistently throughout the study.

The use of oral and IV contrast media should, as long as it is clinically possible, be kept consistent. MRIs of the abdomen, and pelvis with non-contrast CT scan of the chest may be used in participants for whom CT scans with contrast are contraindicated (i.e., participants with contrast allergy or impaired renal clearance).

If a CT scan for tumor assessment is performed using a positron emission tomography (PET)/CT scanner, the CT should be of identical diagnostic quality as a full-contrast diagnostic CT scan.

Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits.

In case of clinically measurable superficial (such as skin) lesions, repeated photographs should be used to document tumor response. These photos must include a ruler for documentation purposes. Participants with known or suspected bone metastases should undergo radionuclide bone scanning.

At the Investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

The data collected for RECIST v1.1 may be used by the Sponsor to calculate time point responses for iRECIST, a recently published set of guidelines developed by the RECIST working group in an effort to harmonize immune-based response criteria across the academic and industrial cancer immunotherapy field (Seymour et al 2017; Appendix 9).

Time point responses will also be calculated for hepatic and extra-hepatic lesions separately according to RECIST v1.1 and optionally iRECIST.

In addition to RECIST v1.1 and iRECIST, further analysis of the CT/MRI scans might be performed by the Sponsor to further elucidate the drug effect. For that purpose, the CT/MRI images collected for RECIST v1.1 will de-identified at the site and securely transmitted to the Sponsor.

Because of possible delayed onset of tumor response associated with immunotherapy treatment, as well as borderline progression, apparent radiologic progression with improving clinical status or mixed responses, in the absence of clinical deterioration, any initial assessment of radiological progressive disease should be confirmed by a repeat evaluation at the next time point for tumor assessment. As with other immunotherapies, treatment beyond 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.

Participants who permanently discontinue study treatment without radiologically defined progression will continue tumor radiological assessments in the post treatment follow-up phase until disease progression is confirmed or a new anti-cancer therapy is started.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Safety assessments will consist of monitoring and recording AEs, including serious adverse events (SAEs) and non-serious adverse events of special interest (NSAESI), measurement of protocol-specified safety laboratory assessments, measurement of

protocol-specified vital signs, ECGs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.2.1 Physical Examinations

A complete physical examination will be conducted at screening and at the end-of-treatment period, and will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, neurological, and musculoskeletal systems in addition to head, eyes, ears, nose, throat, neck and lymph nodes. Examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF.

At other visits, limited, symptom-directed physical examinations should be performed when clinically indicated. Changes from baseline abnormalities should be recorded in participants' notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height and weight will be recorded at the time points indicated in the SoA (Section 1.3).

8.2.2 Vital Signs

Vital signs (temperature, *heart* rate, respiratory rate, *oxygen saturation,* and *systolic and diastolic* blood pressure) will be assessed after the participant has been resting in a supine or sitting position for a period of at least 5 minutes prior to a blood draw or at least 10 minutes following a blood draw. Blood pressure (systolic and diastolic), *heart* rate, respiratory rate*, oxygen saturation,* and body temperature (oral or tympanic) will be recorded at the time points specified in the SoA (Section 1.3).

Blood pressure and pulse measurements will be assessed with a well-calibrated automatic instrument with a digital readout. Manual techniques will be used only if an automated device is not available. When measuring blood pressure, the participant's arm should be unconstrained by clothing or other material and the participant should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). The ideal cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2).

8.2.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and QT corrected for heart rate (QTc) intervals. 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 blood draws for PK/PD samples at the same time point. In case of an absolute QTc of >500 msec and an increase from baseline QTc >60 msec, another triplicate ECG must be recorded within the next 30 minutes. It may be appropriate to repeat abnormal ECGs to rule out improper lead placement potentially contributing to the ECG abnormality.

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

ECG characteristics, including heart rate, QRS duration, pulse rate, and QT intervals, will be recorded on the eCRF. QTcF (Fridericia's correction) and RR interval will be automatically calculated and recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

8.2.4 Echocardiogram/MUGA

Participants will undergo evaluation of left ventricular ejection fraction (LVEF), either by echocardiogram, or MUGA, at specified time points during the study (see SoA in Section 1.3), and as clinically indicated for new or worsening symptoms. Any participant who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF re-assessment and further cardiovascular consultation, as needed. Evaluation of left ventricular function must be performed using the same method for each participant. In case the MUGA scan cannot be replaced by an Echocardiogram, the scan must be performed at least 3 days prior to C*ycle* 1 D*ay 1* and at least 3 days prior to the fresh tumor biopsy, if applicable, to allow collection and immediate shipments of sensitive PD/biomarker samples (i.e. tumor biopsies, PD whole blood FACS).

8.2.5 Ophthalmological Examination

All participants should have a comprehensive ophthalmological evaluation, including medical history (applicable at baseline) and physical examination related to eye disorders, visual acuity, visual field testing, and ophthalmoscopy (including dilated fundoscopy at the timepoints indicated in the SoA (Section 1.3).

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 findings that 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), the results must be recorded in the eCRF.

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

If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

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 PCR Testing for Participants with Resolved Hepatitis B and Hepatitis C

Participants with active, past or resolved hepatitis B infection who are admitted to the study will undergo periodic PCR testing to exclude HBV replication during the study. Similarly, periodic HCV RNA test will be performed during the study for participants who have tested positive for HCV antibody but negative for HCV RNA at study entry.

Frequency of periodic PCR testing for HBV and HCV is provided in the SoA (Section 1.3).

8.2.8 Medical History and Demographic Data

Medical history includes demographics, history of malignancy, previous treatment(s) for malignancy, concomitant diseases, previous surgeries, medication, allergies, reproductive status, alcohol consumption, and smoking habits.

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

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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 60 days after the final dose of study treatment.

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, defined as 60 days after the last dose of study drug or until the start of another anti-cancer therapy, whichever comes first.

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

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions 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 30 days after the final dose of RO7119929 or 3 months after the final dose of tocilizumab, as applicable (whichever is longer).

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 30 days after the final dose of RO7119929 or 60 days after the final dose of tocilizumab, as applicable

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

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

8.3.6 Non-Serious Adverse Events of Special Interest

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:

- 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.
- Hepatitis, including AST or ALT $>$ 10 $\times$ ULN or cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 6 of Appendix 3.
- Grade $\geq$3 hematology lab abnormalities (e.g., lymphopenia, neutropenia, leukopenia)

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

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

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

Not applicable.

8.3.9 Management of Specific Adverse Events

Guidelines for management of specific adverse events are provided in Table 9.

For dose modifications, please refer to Section 6.6.

Table 9 Guidelines for Managing Specific Adverse Events

Event	Action to Be Taken	*Actions for Next Dose of Study Medication*
Cytokine Release Syndrome (CRS) Grade 1 (Fever with or without constitutional symptoms)	• Symptomatic management of constitutional symptoms including paracetamol and antiemetics	• Continue treatment at the next planned dose upon resolution of symptoms • *Consider pre-medication with paracetamol 500-1000 mg PO or IV at the time of drug administration, followed by 500-1000 mg paracetamol PO or IV 4-6 hours after first drug administration.*
CRS Grade 2 (Fever, hypotension responding to fluids; hypoxia responding to <40% O_2)	• *Follow CRS Grade 1 recommendations* • *Monitor cardiac and other organ function closely (in ICU if appropriate)*[1] *manage constitutional symptoms and organ toxicities as required* • For hypotension: IV fluid bolus *250–500 mL* as needed, *based on hemodynamic status per Investigator's clinical judgment* • *For hypoxia: Treat with low-flow oxygen*[3] • *For refractory or unstable hypotension or prolonged CRS Grade 2 (>2 days), or in participants with significant symptoms and/or comorbidities (per Investigators discretion, e.g., impaired cardiovascular function, reduced pulmonary reserve), consider administration of tocilizumab and/or corticosteroids (e.g., methylprednisolone 2 mg/kg/d or dexamethasone 10 mg IV every 6 hours).* [4] • *Collect cytokine panel (unscheduled PD plasma samples) per schedule of assessments in Section 1.3*	• May receive next planned dose if symptoms resolve to Grade ≤1 for three consecutive days. *The dose for the subsequent administration should be discussed* with *the* Medical Monitor. • *H*ospital monitoring for the next dose *for 8-24 hours after dosing* [2] • *Administer pre-treatment with 500 mL crystalloid fluid and paracetamol 500-1000 mg PO or IV at the time of drug administration (±30 minutes), followed by 500-1000 mg paracetamol PO or IV 4-6 hours after first drug administration.*

Event	Action to Be Taken	*Actions for Next Dose of Study Medication*
CRS Grade 3 (Hypotension managed with one pressor; hypoxia requiring ≥40% O_2)	• *Follow CRS Grade 1 recommendations* • *Recommend admission* to ICU for hemodynamic *and organ function* monitoring[1] • *F*or hypotension*:* IV fluid *bolus as described in Grade 2* and vasopressor *support* as needed • *For hypoxia: Treat with low-flow oxygen* [3] • *Administer tocilizumab and IV corticosteroids (e.g., methylprednisolone 2 mg/kg/d or* dexamethasone 10 mg IV every 6 hours [4] • *Collect cytokine panel (unscheduled PD plasma) per schedule of assessments in Section 1.3* • *Hospitalization until complete resolution of signs/symptoms*	• *May receive next planned dose if symptoms resolve to Grade ≤1 for three consecutive days and positive benefit risk assessment by the Investigator in consultation with the Sponsor. The dose for the subsequent administration should be discussed with the Medical Monitor.* • *Hospital monitoring for the next dose for at least 24 hours after dosing*[2] • *Administer pre-treatment with 500 mL crystalloid fluid and 500-1000 mg paracetamol PO or IV at the time of drug administration (±30 minutes), followed by 500-1000 mg paracetamol PO or IV 4-6 hours after first administration*
CRS Grade 4 (Life-threatening consequences; urgent intervention indicated)	• *Follow CRS Grade 3 recommendations* • *Participant requires* ICU admission and hemodynamic monitoring*, and/or mechanical ventilation, and/or* IV fluids and vasopressors as needed	• Discontinue treatment
Other non-hematologic toxicities: Grade 3 or 4	• Hold all study treatments until improvement to Grade ≤1 or baseline • If improvement to Grade ≤1 or baseline does not occur within 3 weeks, discontinue study treatment. Longer delays may be allowed after approval from the Sponsor in cases where the participant is deriving clinical benefit from treatment and the Investigator and Sponsor both feel that the benefits of continued treatment outweigh the risks.	

CRS=cytokine release syndrome; ICU=intensive care unit; IV=intravenous; *PO=orally (per os).*

Note: A hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia.

1 *If Grade ≥2 CRS is observed after administration of RO7119929 at any given dose, the participant should be hospitalized and observed by regular vital sign monitoring until complete resolution of symptoms. Documentation of vital signs including oxygen saturation in the eCRF is required at least every 2-4 hours and as clinically indicated.*

2 *Vital sign monitoring hourly for the first 8 hours, then every 4 hours if participant continues to be hospitalized, and as clinically indicated*

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

4 *Tocilizumab should be administered at a dose of 8 mg/kg IV (8 mg/kg for participants ≥30 kg weight only; 12 mg/kg for participants< 30 kg weight; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (up to a maximum of four doses); refer to Appendix 13, Schedule of Activities for Tocilizumab Treatment for Severe or Life-Threatening Cytokine Release Syndrome.*

CRS is by definition a syndrome that could present with a variety of signs or symptoms including pyrexia (with or without chills), rigors, dyspnea, tachypnea and hypoxia, hypotension, tachycardia, GI symptoms (nausea, vomiting, anorexia, and diarrhea), fatigue, myalgia and arthralgia, rash, and headache. For all events with clinical presentation of CRS after RO7119929 administration, the event should be reported using the preferred term “cytokine release syndrome” and not “flu like symptoms”. It is anticipated that with the mechanism of action of RO7119929, clinical signs and symptoms of CRS will be actually dependent on a systemic increase of cytokines, and therefore the most appropriate term for reporting is “cytokine release syndrome”.

Consistent with the TLR7 mechanism of action, CRS and flu like symptoms have been reported with systemic TLR7 agonists and IFN-α therapies in humans. In general, these symptoms were dose-dependent and commonly reported as flu like symptoms (Dudek et al 2007, Dummer et al 2008, Meyer et al 2008, Geller et al 2010, Gane et al 2015, Agarwal et al 2018). Only rare cases of CRS associated with hypotension requiring hospitalization and intravenous infusion have been reported with TLR7 agonists after the first dose (including a case of 5-fold overdosing) or second dose (Goldstein et al 1998, Janssen et al 2018, Fidock et al 2011). Only two cases with grade 3/4 CRS have been reported in the literature to date. These subjects were treated with a TLR7/8 dual agonist, and treatment was subsequently discontinued in one subject. No corresponding cytokine data have been published, and thus the correlation between systemic cytokine levels in humans after TLR7 agonist administration and occurrence of high grade CRS are unknown (Gupta et al 2017).

In vitro tests with RO7117418, the active drug of the pro-drug RO7119929, as well as in vivo tests with RO7119929 in cynomolgus monkeys showed a dose-dependent release of different pro-inflammatory cytokines including IFN-α, IP-10, TNF-α, and IL-6, a pattern in line with the mode of action expected for a TLR7 agonist (O’Neill et al 2013).

*Based on the clinical and biomarker results gathered from the participants treated in Part A Schedule 1, CRS has been identified as a dose-dependent risk for treatment with RO7119929, and high levels of IL-6 have been observed in participants developing CRS Grade ≥ 2 (*see the Investigator’s Brochure for details*).*

For the management of AEs specific to tocilizumab, see the Investigator’s Brochure and local prescribing information.

8.4 TREATMENT OF OVERDOSE

Any dose, which is above the planned dose (e.g., the weekly dose taken at once), will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate plasma concentrations of study treatment RO7119929 and its metabolite, RO7117418 (active drug) will be collected. The date and time of each sample collection will be recorded in the eCRF. RO7119929 and RO7117418 levels will be analyzed by using validated assays. The PK samples will be taken as outlined in the SoAs (see Section 1.3). During the course of the study, PK sampling time-points may be modified based on emerging data to ensure the pharmacokinetics of RO7119929 and RO7117418 can be adequately characterized. Unscheduled PK samples will be taken at the time of the development of any events listed in Section 4.2.3.

- RO7117418: Metabolite (active drug) is measured by a specific validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.
- Any volume of blood samples remaining after the specified analyses may also be used for retrospective and longitudinal testing of SARS-CoV-2 or other bacterial or viral infections (see Section 8.7) with serological methods or additional validation experiments, e.g., exploratory metabolite identification.

The PK blood samples will be destroyed after the date of final clinical study report or after approval by the study management team, or earlier depending on local regulations. Details on sampling procedures, sample storage, and shipment are given in the sample documentation.

8.6 IMMUNOGENICITY

Not applicable.

8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

The PD outcome measures for the dose escalation Part A of this study are:

- Whole blood samples (PD blood [RNA], see Section 1.3) will be analyzed for RO7119929 mediated, dose/exposure dependent changes in interferon stimulated genes such as, but not limited to ISG15 but also MX1 and OAS1 in Cycle 1 and Cycle 2.
- Cytokine induction such as IFN-α will be monitored in plasma for RO7119929 mediated, dose/exposure dependent changes (PD plasma [safety], PD plasma, see Section 1.3) and in the context of safety related pharmacodynamic changes, in IL-6, IL-8, IP-10, TNFα and sCD25 at the same time points in Cycle 1 and Cycle 2.
- One pre- and on-treatment whole blood sample (PD blood [DNA], see Section 1.3) will be collected for PoM gated analysis of changes in the peripheral T cell Vβ repertoire. This may serve as a surrogate marker for tissue related PoM.
- Whole blood pre-treatment DNA samples (blood [DNA], see Section 1.3) will be assessed for gene polymorphisms including but not limited to TLR7, CYP2C9, CYP2C19, UGT1A9, and UGT1A1 as potential response or safety prediction markers.

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

In addition to PD sampling in Part A, the PoM PD outcome measures for Part B of this study are:

- Paired fresh pre-treatment (baseline/screening) and on-treatment biopsies (Cycle 2 Day 2) from the hepatic tumor manifestation are mandatory for all participants *in the expansion part of the study (Part B see* Section 1.3 and Section 8.8.1.3). Tissue will be assessed for changes *associated to the immune system (e.g.,* immunostimulatory cytokines/chemokines*)* via RNA based analysis, number, activation status and spatial location of TILs, as well as additional tumor markers such as PD-L1 and FAP expression. Additional exploratory protein, DNA or RNA based analysis to identify potential response prediction or resistance biomarkers may be performed on residual tissue.
- Immunophenotyping using protein based analysis methods from whole blood samples (PD whole blood FACS, see Section 1.3) to characterize the phenotype and functional status of peripheral immune cells will be performed from all participants in Part B.

Response prediction markers for Parts A and B of the study are:

- Archival tissue (if available) must be submitted within 2 months of enrollment to allow for genetic and genomic analysis described in Section 8.7.1 and any immune cell characterization as described for the fresh biopsies to identify potential response prediction or resistance biomarkers.

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

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

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

These samples will be destroyed within 5 years after the date of final clinical study report unless the participant gives specific consent for the remainder of the sample(s) to be stored for optional exploratory research within the RBR (see Section 8.9).

8.7.1 Genetic and Genomic Analyses

Whole blood samples for genetics will be taken at the time-points mentioned in SoA (see Section 1.3). These samples will be destroyed no later than 5 years after the date of final clinical study report, unless the participant gives specific consent for the remainder of the residual material to be stored for optional potential exploratory research within the RBR (see Section 8.9).

Residual tissue of fresh paired tumor biopsies as well as archival tissue material may be used for exploratory genomic analysis.

The results of such specimen analysis will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future. The specimens will also be made available for future biomarker research towards further understanding RO7119929, treatment of related diseases and AEs.

For related pharmacogenomics or genetic analysis, see RBR (Section 8.9).

8.7.1.1 Clinical Genotyping

DNA may be used to identify biomarkers that are predictive of response to treatment with RO7119929, and will help to better understand the pathogenesis, course, and outcome of the studied cancer types. The DNA may be used for, but analysis is not limited to:

- Genetic variants of cytochrome P450s (e.g., CYP2C9, CYP2C19, CYP3A4, CYP3A5, UGT1A9, UGT1A1), transporters (e.g., multi-drug resistance 1 [MDR1]), or receptors which might affect the metabolism, pharmacokinetics, pharmacodynamics, safety of RO7119929.
- Genetic variants of the TLR7 gene.
- Genetic variants of pathways related to TLR7, HCC or other tumor types included into the study, including but not limited to, genes related to disease/efficacy, safety, PK, or PD parameters of RO7119929.
- Genes coding for human leukocyte antigens (i.e., human leukocyte antigen [HLA] gene family).

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

8.7.1.2 Whole Genome/Exome/Targeted DNA Analysis

Archival tumor tissue, fresh tumor tissue sample and blood will be collected at the visits specified in the SoA (Section 1.3) and may be used for DNA and/or RNA extraction for exploratory research on genomic biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways, or immune-related

markers such as T-cell receptor sequence/TCR Vβ, microsatellite instability [MSI] and tumor mutation burden [TMB]).

Samples collected for DNA extraction (see Section 8.8) include, but are not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS 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.

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

Transcriptome Analysis

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

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

8.8 PHARMACODYNAMICS AND BIOMARKER SAMPLES

All PD/biomarker samples may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to RO7119929, identifying biomarkers useful for predicting and monitoring RO7119929 safety, assessing pharmacodynamic effects of RO7119929 and investigating mechanism of therapy resistance. Additional markers may be measured in the case that a strong scientific rationale develops.

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

Based on continuous analysis of the data in this study and other studies, any sample type and/or analysis 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.

- Unless otherwise specified below, samples (including blood, slides, extracts, etc.) will be destroyed no later than 5 years after the date of final clinical study report. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.9).
- Any remaining blood/serum/plasma or tissue samples after the specified analyses may also be used for additional (assay) validation experiments. Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to TLR7 activation, characterization of the tumor/immune contexture, pre-existing and acquired immune inhibitory or stimulatory pathways.
- Details on processes for collection and shipment of these samples can be found in separate sample documentation.

8.8.1 Mandatory Samples

All samples for PD and biomarker research outlined in the SoA*s* (Section 1.3) and in Section 8.7 are required and will be collected from all participants.

8.8.1.1 Blood Sampling

Samples will be collected for measurement of peripheral cytokine/chemokine release, expression of interferon stimulated genes as well as safety related cytokines (Part A and B), immun*o*phenotyping (only Part B) and to assess response prediction markers as outlined in the SoA*s* (Section 1.3) and in Section 8.7. A mandatory whole blood sample will be taken for DNA extraction and clinical genotyping from every participant. If the sample is missed on Day 1, it can be collected at any other scheduled visit.

8.8.1.2 Optional Samples

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

8.8.1.3 Tissue Sampling

Archival Tumor Samples

Formalin-fixed paraffin embedded (FFPE) archival tumor tissue is *mandatory and* to be obtained from all participants enrolled in Part A and B, if available. These samples are from the primary tumor or, if not available, from a prior metastasis. Samples will be collected for measurements as given in Section 8.7.

The provision of archival FFPE blocks is preferred, but if not possible, a minimum of 4 slides is recommended in order to perform the T cell infiltration analysis.

For enrolled participants, remaining archival tissue blocks will be returned to the site no later than the time of final closure of the study database or upon request, whichever occurs first. For participants who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination. Other residual

tissue material (may include blood, serum samples and slides, extracts, on-study blocks, etc.) will be destroyed within 5 years after the date of final clinical study report.

Fresh Tumor Biopsies

Mandatory fresh tumor biopsy samples will be collected from a safely accessible site within the liver from all participants enrolled in Part B of the study on two occasions: at baseline and once during the study treatment period [C*ycle* 2 D*ay* 2] (see Table 3 *and Table 5*). Each sample will consist of at least three core tissue specimens. Collection of tumor biopsy samples will be guided by ultrasound or CT scan using a 16-gauge needle to provide cores of at least 20 mm in length.

Cytological, fine needle aspiration or biopsy of bone lesions or any extra-hepatic tumor manifestation is not acceptable.

The baseline and on-treatment biopsies should preferably be taken from the same accessible, “non-critical” tumor lesion (metastasis) within the liver to ensure comparability. If feasible, on-treatment biopsies may be repeated if the initial biopsy did not contain sufficient tumor material for analysis. If preliminary data suggest, alternative on treatment tumor biopsy time points may be considered upon joint agreement between Investigators and the Sponsor.

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 a diagnostic biopsy and participants should not have received any tumor treatment after this collection).

Optional Tissue Sample

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. A separate signature will be required to document a participant's agreement to allow any remaining samples to be used for exploratory research (see Section 8.9.1.2).

An additional biopsy at the time of disease progression, partial response, stable disease, or at any other time point of interest based on participant’s course of disease may be taken after discussion between the Investigator and the Sponsor, to aid the understanding of resistance mechanisms.

8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.9.1.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of the RBR samples will facilitate the rational design of new pharmaceutical agents and the

development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

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

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

8.9.1.2 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7119929:

- RBR (DNA/RNA) sample
- Leftover plasma samples
- Leftover serum samples
- Leftover blood samples
- Leftover blood samples for DNA extraction
- Leftover tumor tissue (fresh pre- and on treatment tumor tissue)

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

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 of germline or somatic mutations via WGS/WES, or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new

therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Participants will not be identified by name or any other personally identifying information. Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For all samples, dates of consent and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

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

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

8.10 HEALTH ECONOMICS/MEDICAL RESOURCE UTILIZATION

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

8.11 TIMING OF STUDY ASSESSMENTS

8.11.1 Screening and Pre-treatment Assessments

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

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

An Eligibility Checklist 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 Cycle 1 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

Cycle 1 Day 1 (unless otherwise specified) may be used (and do not need to be repeated for screening).

8.11.2 Assessments during Treatment

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

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

8.11.3 Assessments at Study Completion/Early Termination Visit

Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit and may undergo follow-up assessments (see Section 8.11.4), unless the participant withdrew consent.

Participants who complete study treatment (defined as 12 months of treatment within the study) or discontinue from the study early will be asked to return to the clinic within 28 days after the final dose of study drug for an EOTV. The visit at which response assessment shows progressive disease may be used as the study completion/early termination visit.

8.11.4 Follow-Up Assessments

Participants will be treated until disease progression, unacceptable toxicities, or withdrawal of the participant's consent. Participants may continue study treatment for a maximum of 12 months. This time period can be prolonged if the participant derives a clinical benefit from the treatment after discussion with the Medical Monitor and approval by the Sponsor.

As with other immunotherapies, treatment beyond RECIST progression may be considered following discussion between the Investigator and the Sponsor (see Section 7.1). The criteria needed for continuing treatment beyond initial apparent progressive disease per RECIST v1.1 (e.g., radiological progression secondary to tumor inflammation) are outlined in Section 8.1.1.

After the study completion/early termination visit, adverse events should be followed as outlined in Section 8.3.1 and Section 8.3.3, including a Safety Follow-Up Visit 60 days after the final dose of study drug.

Thereafter, the sites will provide to the Sponsor an update on survival status and post-study anti-cancer therapies as outlines in the SoA (Section 1.3).

8.11.5 Assessments at Unscheduled Visits

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

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Not applicable.

9.2 SAMPLE SIZE DETERMINATION

Approximately 35 to 40 evaluable participants will be included *under each schedule for* dose escalation Part A. The exact number of participants will depend on the occurrence of DLTs and the number of dose-levels required to determine the MTD and/or the RDE. Based on study simulations assuming a variety of potential dose-toxicity profiles, the estimated chance to require more than 45 evaluable participants is below 10%. The maximum number will be 60 DLT-evaluable participants.

An analysis of RO7119929 effects in the tumor microenvironment is an important endpoint for demonstrating PD proof of mechanism in this study. This analysis will require paired tumor biopsies prior to and following RO7119929 dosing for each participant in study Part B. Participants with both tumor biopsy samples available and evaluable will be considered evaluable for this PD endpoint. The design for study Part B specifies up to approximately 30 PD-evaluable participants. Based on an anticipated 50% success rate for obtaining paired tumor biopsies, it is expected that up to approximately 60 participants will be enrolled in the study expansion Part B.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in *Table 10*.

Table 10 Analysis Populations

Population	Description
Efficacy	All participants who received at least one dose of RO7119929 and had at least one tumor assessment.
Safety	All participants who received at least one dose RO7119929, 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 RO7119929 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 and disease history) will be analyzed using descriptive statistics. The analysis will be based on the safety analysis population. Data will be summarized by cohort and regimen within each part.

9.4.2 Efficacy Analyses

No formal statistical model and no formal hypothesis testing are planned in this study. Efficacy analysis will be performed for all participants in the efficacy analysis population and grouped according to dose cohort within each study part. Tumor response data will be reported for RECIST v1.1 and for iRECIST using descriptive statistics. Objective response and disease control rates will be summarized using relative frequencies and 90% confidence limits. Duration of response and progression-free survival (PFS) will be summarized using time to event analyses and Kaplan-Meier curves.

9.4.3 Safety Analyses

The primary endpoint of the study will be safety and, in particular, the occurrence of a DLT. All participants enrolled in the study who received at least one dose of study medication will be included in the safety evaluation. DLT will be evaluated *for the first* 3 weeks *in Schedules 1 and 3 and for the first 4 weeks in Schedule 2.* In order to be evaluable for DLT, participants *in Schedule 1 and 3* need to have taken in all three doses scheduled within Cycle 1*, and participants in Schedule 2 need to have taken in all four doses planned within the first 4 weeks. In case a second dose of tocilizumab is introduced into Schedule 3 at Cycle 1 Day 15, participants also need to have taken in all four doses planned within the first 4 weeks to be evaluable for DLT*. Participants experiencing a protocol-defined DLT already with fewer doses are also DLT-evaluable. Dose escalation will be guided by the CRM-EWOC design, which will target identification of the MTD. The model will be estimated using Bayesian inference with a minimal informative prior for the model parameters. Details on the statistical model, the priors and the dose escalation algorithm are defined in Appendix 6. Safety will be characterized by AEs, laboratory tests, vital signs, ECG, physical examinations and performance status, as well as by DLTs. Descriptive statistics will be used to summarize all safety data by dose cohort, by schedule, and overall within the respective study parts.

Table 11 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.
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 from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. For details on standard reference ranges and data transformation and the definition of laboratory abnormalities, see Appendix 4.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate.
Concomitant medications	The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented in summary tables and listings.

9.4.4 Pharmacokinetic Analyses

PK parameters will be derived from the plasma concentrations and will be listed and summarized using descriptive statistics including means, geometric means, standard deviations, and coefficients of variation. The parameters will include, e.g., area under the curve (AUC), clearance (CL), Vss, accumulation ratio and terminal elimination half-life. Estimation of PK parameters may be performed using standard non-compartmental methods and/or population PK modeling. If data allow, other exploratory methods may be used for data analysis, e.g. PK and PD data may be used to develop a population PK/PD model.

Actual sampling times are presented in the SoA (Section 1.3). Individual and mean concentration versus time will be plotted on either semi-logarithmic or normal scales. The linearity of PK (AUC and maximum concentration [C_{max}]) will be investigated. In order to assess the food effect on pharmacokinetics of RO7119929, PK parameters will be analyzed for a minimum of 6 participants (see Section 5.3.1).

9.4.5 Immunogenicity Analyses

Not applicable.

9.4.6 Pharmacodynamic Analyses

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

Descriptive statistics will be used to summarize peripheral blood and tumor PD markers. Absolute and percentage change from baseline will be calculated for the PD markers. Graphical techniques will be employed to better understand the relationship of the PD markers with dose and time. Correlations between PK parameters, PD markers and clinical response will be assessed through data tabulations and graphical techniques.

9.4.7 Other Analyses

Exploratory analysis may also be performed to identify markers and/or marker panels correlating with and/or potentially predictive of an in vivo PD response and the occurrence of certain AEs.

9.5 INTERIM ANALYSES

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

9.6 SUMMARIES OF CONDUCT OF STUDY

All reportable deviations will be listed.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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.

Consent to Participate in the Research Biosample Repository

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

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

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

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

Approval by the Institutional Review Board or Ethics Committee

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

Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant’s wishes using the RBR Withdrawal Form and, if the 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 WP41377 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant’s withdrawal from the RBR does not constitute withdrawal from Study WP41377. 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 samples must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

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

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

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

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

Monitoring and Oversight Research Biosample Repository

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

review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5. FINANCIAL DISCLOSURE

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

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

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

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

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

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

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

2.1.2. Clinical Outcome Assessment Data

2.1.2.1 Paper Clinical Outcome Assessment Data

All original forms on which participants records responses are source documentation as described in Section 2.1.3. of this Appendix.

2.1.2.3. Safety Biomarker Data

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

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

2.1.3. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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 participant or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

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

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

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

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

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

2.3.3. Dissemination of Clinical Study Data

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

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

2.3.4. Site Inspections

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

3. ADMINISTRATIVE STRUCTURE

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

4. STUDY AND SITE CLOSURE

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

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

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

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

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

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

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

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

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:

- 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 Medical Monitor. 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 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 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale

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

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

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

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

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

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

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

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 6 for reporting instructions), per the definition of serious adverse event in Section 2.

3.2. ASSESSMENT OF CAUSALITY

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

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

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

4. FOLLOW-UP OF AES AND SAES

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

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

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

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

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5)
- DLTs during the DLTs assessment window (see Section *4.1.4*).

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

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

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

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

Events that Occur prior to Study Treatment Initiation

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

Events that Occur after Study Treatment Initiation

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

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

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

Reporting of Post-Study Adverse Events and Serious Adverse Events

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

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

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For RO7119929 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 RO7119929 regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and should be recorded as described below:

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

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

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

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

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

- RO7119929 Investigator’s Brochure
- RO4877533 (Tocilizumab) Investigator’s Brochure

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

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

Appendix 3
Procedures for Recording Adverse Events

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

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

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. CYTOKINE RELEASE SYNDROME

For all events with clinical presentation of CRS after RO7119929 administration, the event should be reported using the preferred term “cytokine release syndrome” and not “flu like symptoms.” It is anticipated that with the mechanism of action of RO7119929, clinical signs and symptoms of CRS will actually dependent on a systemic increase of cytokines, and therefore the most appropriate term for reporting is “cytokine release syndrome.”

1.2. OTHER ADVERSE EVENTS

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 × baseline value) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). The patient population for this study consists of patients with decreased hepatic function who may exhibit abnormal liver function test results, some of which may meet Hy's law criteria prior to enrollment in the trial. The following modified Hy's law criteria are for the purpose of determining what may constitute a drug-induced liver injury for this trial population and define those cases which require expedited reporting to the health authorities in relation to Hy's law. Investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin ≥ 2 × ULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3× baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF 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 an adverse event of special interest (see Section 8.3.4).

7. DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2) that are attributed by the Investigator solely to progression of the condition being studied 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 CONDITION BEING STUDIED

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on criteria (e.g., RECIST). 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.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory unless otherwise specified. If the local laboratory results are used, the results must be captured in source documentation and entered into the eCRF.

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

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

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells), and platelet count
Clinical Chemistry	• Sodium, potassium, magnesium, chloride, bicarbonate, glucose (non-fasting), BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, ALP, CRP, urate, LDH, lipase.
Coagulation	• INR, aPTT, PT.
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), HBs antibody, hepatitis C virus (HCV) antibody, and PCR for HBV and HCV.
Thyroid Hormones	• TSH, free T3 (or T3), free T4
Myocardial markers	• Cardiac troponin I or cardiac troponin T and BNP or NT-proBNP, with intra-patient consistency
Autoimmune antibodies	• ANA screen, anti-double-stranded DNA antibodies, cytoplasmic anti-neutrophil cytoplasmic antibody, perinuclear anti-neutrophil cytoplasmic antibody
Pregnancy Test	• All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at specified timepoints. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Urinalysis	• Glucose, protein, urobilinogen • 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.

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
- Potential analysis considerations for analyzing Laboratory data includes the use of Standard Reference Ranges and potential transformation of data for specific lab tests.
- In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

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

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

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

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 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]

d) 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.

e) 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 the SoA (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 while the male participant is in this study (see Section 8.3.5 Pregnancy). This applies only to male participants who receive study treatment.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- 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).

Appendix 6
Statistical Model Dose Evaluation

This appendix provides details of the design that will guide the RO7119929 dose escalation stage of this study and of its operating characteristics through simulations. All analyses were performed using the R statistical software R version 3.5.1 (2018-07-02) (R Core Team [2017]) (see Section 2 for additional information).

1. RATIONALE FOR MODEL BASED DESIGN

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

In this design, the MTD is defined as the dose maximizing the posterior probability that the DLT rate, π(MTD) ϵ [0.2, 0.35] while keeping the probability of overdose P{p(MTD) $>$0.35} $<$0.25.

2. STATISTICAL MODEL

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

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

where

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

and d* is the reference dose (in this case d* = 10 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.

2.1. GENERAL MODEL SETTING

2.1.1 Dose Grid

The following dose grid has been used: From 1 mg to 10 mg by 1 mg; from 10 mg to 20 mg by 2 mg; from 20 mg to 50 mg by 5 mg; from 50 mg to 150 mg by 10 mg; from 150 mg to 250 mg by 25 mg.

2.1.2. Maximum Dose Increments

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

Maximum Dose Increments Relative to Dose Levels:

- From 0 mg up to 10 mg a 200%, from above 10 mg up to 60 mg a 100% and above 60 mg a 50% maximum increments respectively are allowed.

Maximum Dose Increments Relative to DLT:

- Until 1 DLT an increment of 200% and from 1 DLT an increment of 100% maximum are allowed.

After the two rules have been applied the maximum allowed dose increment will be defined as the lower increment of the two resulting increments.

2.2. STOPPING RULES

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

- **Enough information on MTD:**

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

- **Maximum dose is safe:**

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

- **Maximum number of participants:**

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

2.3. Model Prior

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

This minimally informative prior "neutral" component will be constructed based on the assumed not toxic and toxic dose levels. It is conservatively assumed to be very unlikely (with 70% confidence) that a 20% or higher DLT rate is associated with the first dose of RO7119929 dose escalation and to be very unlikely (with 90% confidence) that a 35% or lower DLT rate is associated with the dose of 250 mg.

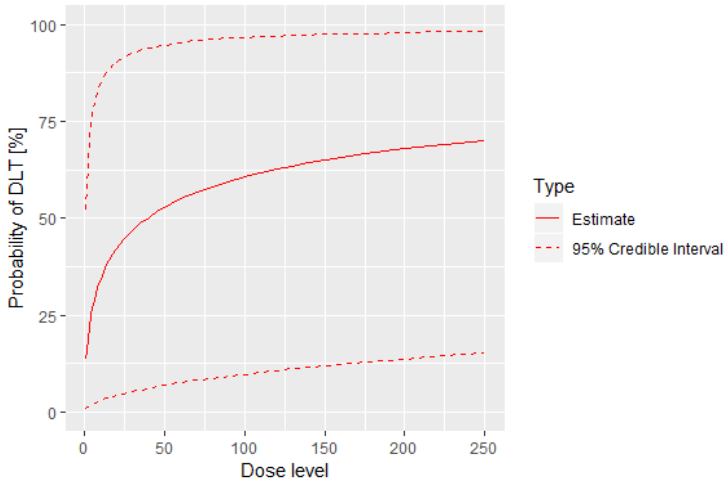
The parameters of the minimally informative prior are listed below (3):

$$\mu = (\alpha, \beta) = (-0.88, 0.64)$$
$$\Sigma = \begin{pmatrix} \sigma_\alpha^2 & \sigma_{\alpha\beta} \\ \sigma_{\alpha\beta} & \sigma_\beta^2 \end{pmatrix} = \begin{pmatrix} 1.78 & 0.05 \\ 0.05 & 0 \end{pmatrix} \quad (3)$$

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



3. MODEL PERFORMANCE EVALUATION

To illustrate how the design will perform, different escalation scenarios are explored and results are tabulated in Table 1. Each column represents four different situations: which dose would the model recommend, after seeing no DLTs in previous cohorts and when 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 study would be halted.

As it can be seen in Table 1, in general if no DLTs are present, the model will suggest to escalate close to what the maximum increments allow, 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.

Table 1 Model Performance Evaluation

Dose Level	Dose (mg)	Next dose (% increment) if no DLT	Next dose (% increment) if 1 DLT	Next dose (% increment) if 2 DLTs	Next dose (% increment) if 3 DLTs
1	1	3 (200%)	1 (0%)	stop	stop
2	3	9 (200%)	4 (33%)	1 (-67%)	stop
3	9	25 (178%)	12 (33%)	5 (-44%)	2 (-78%)
4	25	50 (100%)	25 (0%)	12 (-52%)	7 (-72%)
5	50	100 (100%)	60 (20%)	30 (-40%)	16 (-68%)
6	100	150 (50%)	130 (30%)	60 (-40%)	35 (-65%)
7	150	225 (50%)	225 (50%)	110 (-27%)	70 (-53%)

4. SIMULATION STUDY

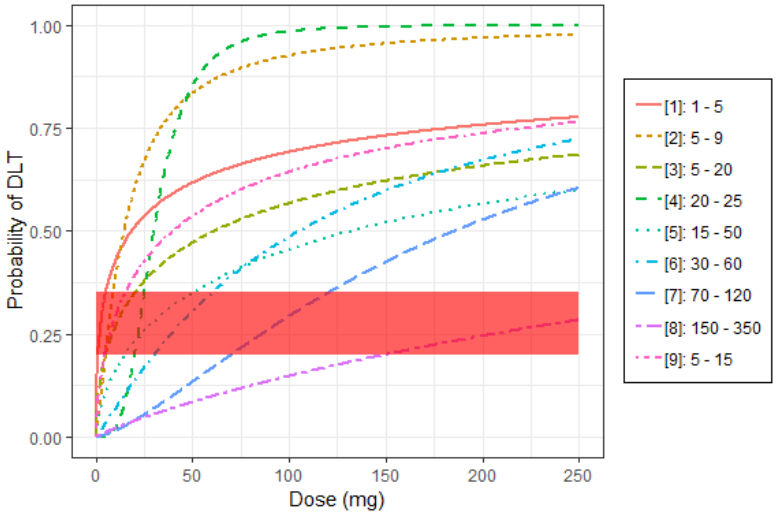
A simulation study is conducted to evaluate the operating characteristics for the chosen design parameters (priors, reference dose, stopping rule) under various dose-toxicity scenarios.

4.1. 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, nine scenarios will be explored. The first eight represent different levels of toxicity from very toxic to a safe, while the last one considers the toxicity depicted in the prior as true toxicity. Some scenarios, especially the scenarios with high toxicity at low doses, are very extreme and not very likely, 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 used for Simulation



4.2. SIMULATION RESULTS

For each of the scenarios, 1000 trials were simulated.

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

From these simulations, it can be seen that the design is able to provide a reliable estimate of the MTD. To be noted, in case of very low toxicity (dose range of target toxicity between150 and 350 mg), the maximum dose is selected as MTD.

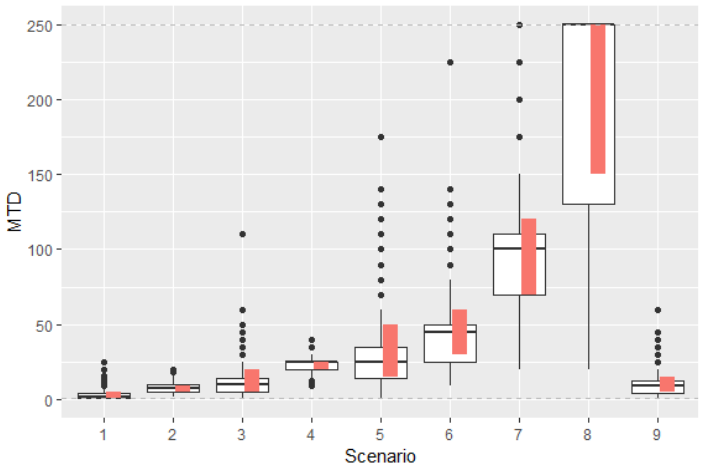
This is also shown in Figure 3, where the distribution of MTDs identified in the various simulation runs is plotted against the true target toxicity range (red bars) for each scenario.

The number of participants treated over the dose toxicity interval is limited and also the sample size required to identify the MTD is reasonable: the median number of participants required to give an MTD recommendation based on cohorts of 3 participants is not larger than 36 participants across all scenarios. In case of high toxicity with low dose levels, the required number of treated participants is even lower.

Table 2 Simulation Results

Scenario	True target dose range	Overall N of participants	N participants treated above target toxicity	Proportion of DLTs in the trials	Dose selected as MTD
1	1 - 5	18 (3, 30)	0 (0, 15)	29.2% (22.2%, 66.7%)	2 (0, 6)
2	5 - 9	27 (18, 39)	6 (0, 12)	25% (20.8%, 30.3%)	7 (4, 10)
3	5 - 20	30 (18, 42)	0 (0, 12)	23.3% (18.2%, 30.6%)	10 (3, 25)
4	20 - 25	30 (21, 36)	3 (0, 9)	20% (18.2%, 23.8%)	25 (16, 25)
5	15 - 50	33 (21, 45)	0 (0, 12)	20% (16.7%, 25.5%)	25 (10, 50)
6	30 - 60	33 (24, 45)	3 (0, 12)	19.4% (16.6%, 24.2%)	45 (25, 70)
7	70 - 120	36 (27, 45)	3 (0, 12)	16.7% (13.3%, 21.4%)	100 (50, 140)
8	150 - 350	33 (27, 45)	0 (0, 0)	12.1% (3.7%, 16.7%)	250 (100, 250)
9	5 - 15	27 (18, 42)	0 (0, 15)	23.8% (19%, 30.8%)	9 (3, 20)

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



4.3. MODIFICATIONS FOR STEP-UP DOSE ESCALATION IN PART A SCHEDULE 2

The modifications to the mCRM to accommodate the step-up dosing in Part A Schedule 2 are as follows. The mCRM model will use the (weighted) average dose across all doses received until the end of the DLT period of 28 days or the occurrence of a DLT, whichever comes first. The outcome of the mCRM model will be the new average of the first four QW doses. Since Cycle 1 Day 1 and Cycle 1 Day 8 doses are fixed (details see Section 4.1.1.1.2), it provides a recommended dose for the target dose to be given on Cycle 1 Day 15. The Cycle 1 Day 15 dose will subsequently be administered QW during each subsequent cycle.

The model will use a non-informative prior and accumulating data from Part A Schedule 1 (flat-dose) and Part A Schedule 2 (step-up dosing) to guide the recommendation for the target dose. For each evaluable patient, a weighted average dose will be calculated. Weights are set such that for each week passed between the event and the dose, the weight for the dose will be halved.

The average dose adjusted for time of dosing is computed as follows:

Example:

Cycle 1 Day 1 dose = 1 mg, Cycle 1 Day 8 dose = 3 mg, Cycle 1 Day 15 dose = 6 mg, and Cycle 1 Day 21 dose = 6 mg

- *Participant with DLT before Cycle 1 Day 8 → Average dose 1 mg*
- *Participant with DLT before Cycle 1 Day 15 → Average dose (1 mg + (2×3 mg))/3 = 2.3 mg*
- *Participant with DLT before Cycle 1 Day 21 → Average dose (1 mg + 2×3 mg + 4×6 mg)/7 = 4.4 mg*
- *Participant with DLT after Cycle 1 Day 21 or without DLT → Average dose (1 mg + 2×3 mg + 4×6 mg + 8×6 mg)/15 = 5.3 mg*

Since the mCRM model for Part A implicitly uses the average dose, the same mCRM model can be used for all dose-escalation parts in this study.

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Appendix 7 Prohibited Co-medications in Respect to RO7119929 Dosing

Table 3 Prohibited Co-medications

Restrictions for RO7119929 dosing	Enzymes	Enzyme Modulation	Co-medications
Prohibited	CYP2C9 and CP2C19 strong and moderate inhibitors	Potential increase of RO7119929 exposure during first pass by inhibiting the conversion of RO7119929 by CYP2C9 and CYP2C19	amiodarone, felabamate, fluconazole, fluoxetine, fluvoxamine, miconazole, piperine, ticlopidine

Table 4 Prohibited Co-medications with Time Window in Respect to RO7119929 Dosing

Restrictions for RO7119929 dosing	Enzymes	Enzyme Modulation	Co-medications
Prohibited co-medication for at least 4h before and 2h after RO7119929 dosing	CYP3A4 moderate and strong substrates	Potential CYP3A inhibition by RO7119929 in the GI tract	alfentanil, alprazolam, aprepitant, avanafil, budesonide, buspirone, colchicine, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eliglustat, eplerenone, everolimus, felodipine, ibrutinib, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, pimozide, quetiapine, rilpivirine, rivaroxaban, saquinavir, sildenafil, sirolimus, tacrolimus, tadalafil, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil
Prohibited co-medication for at least 4h before and 8h after RO7119929 dosing	OATP1B1/OATP1B3 substrates and inhibitors	Potential OATP1B1 inhibition by RO7117418 and potential increase of RO7117418 exposure as it is a OATP1B1 substrate and inhibitor	asunaprevir, atazanavir, atorvastatin, bosentan, cerivastatin, clarithromycin, cyclosporine, danoprevir, docetaxel, erythromycin, fexofenadine, gemfibrozil, glyburide, lopinavir, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rifampin, ritonavir, rosuvastatin, simeprevir, simvastatin
Prohibited co-medications for at least 4h before	UGT1A9 and UGT1A1/1A3 inhibitors	Potential increase of RO7117418	amitriptyline, aurothiomalate, dacomitinib, dasabuvir, deferasirox, diflunisal,

Restrictions for RO7119929 dosing	Enzymes	Enzyme Modulation	Co-medications
and 8h after RO7119929 dosing		exposure as it is mainly metabolized by UGT1A9 and UGT1A1/1A3	eltrombopag, enasidenib, ertugliflozin, flunitrazepam, flurbiprofen, (fos)phenytoin, fostamatinib, glecaprevir, indinavir, indometacin, isavuconazole, ketoconazole, mefenamic acid, niflumic acid, nilotinib, ombitasvir, paritaprevir, pazopanib, pibrentasvir, probenecid, propofol, regorafenib, rucaparib, silibinin, sorafenib, valproic acid

Appendix 8
Response Evaluation Criteria in Solid Tumors – Version 1.1 – Modified Excerpt from Original Publication with Addition of Supplementary Explanations

The following text is based on Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

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, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- “Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. 'However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

1.2.1 Measurement of Lesions

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

1.2.2 Method of Assessment

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

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

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

If prior to enrollment it is known that a participant is unable to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the subject at baseline and during study, should be guided by the tumor type under investigation and the anatomic location of the disease. For participants who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the participant should be considered not evaluable from that point forward.</u>

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

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

2 TUMOR RESPONSE EVALUATION

2.1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess OR or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1.1.1).

2.2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where participants have only one or 2 organ sites involved a maximum of 2 (one site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is $\geq$ 10 mm by CT scan).

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 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' (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 CRF (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

- CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- 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).
- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be

zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

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

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

2.3.3 Evaluation of Non-Target Lesions

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

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

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

PD: Unequivocal progression (Section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4 Special Notes on Assessment of Progression of Non-target Disease

When the participant also has measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-measurable disease: this circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change

in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.4 EVALUATION OF RESPONSE

2.4.1 Time-point Response (Overall Response)

It is assumed that at each protocol specified time-point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time-point for participants who have measurable disease at baseline.

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

Table 1 Time-Point Response – Target (w/wo non-target) Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Time-Point Response – Non-Target Lesions Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = inevaluable; PD = progressive disease; SD = stable disease.

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

2.4.2 Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular time-point, the participant is not evaluable at that time-point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time-point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time-point response. This would be most likely to happen in the case of PD.

For example, if a participant had a baseline sum of 50 mm with 3 measured lesions and during study only 2 lesions were assessed, but those gave a sum of 80 mm, the participant will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the participant is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time-point.

Table 3 Best Overall Response when Confirmation is Required

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

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

2.4.3 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the CRF.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an OR: it is a reason for stopping study therapy. The OR status of such participants is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

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

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

Appendix 9 Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

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

Response evaluation through use of iRECIST requires collection of tumor assessment data after radiographic progression per RECIST v1.1. Details regarding lesion evaluation are described below. When not otherwise specified, RECIST v1.1 conventions will apply.

Criteria for determining overall response at a single time point per iRECIST are also summarized below. Of note, overall response per iRECIST will not be captured in the electronic Case Report Form (eCRF), but will instead be calculated programmatically by the Sponsor on the basis of investigator-assessed individual lesion data recorded in the eCRF.

iRECIST response status is not a specific component of treatment discontinuation criteria, including decisions about whether to continue treatment beyond progression per RECIST v1.1. Investigators should instead take into account radiologic data and clinical status in making such decisions

EVALUATION OF LESIONS TO SUPPORT iRECIST RESPONSE ASSESSMENT AFTER DISEASE PROGRESSION PER RECIST V1.1

iRECIST is an extension of RECIST v1.1 that allows for response assessment following disease progression per RECIST v1.1. RECIST v1.1 rules for categorizing lesions as measurable or non-measurable and measuring lesions also apply to iRECIST. After disease progression per RECIST v1.1, the same target and non-target lesions selected at baseline will continue to be followed, along with any new lesions that develop, to support iRECIST response evaluations, as described below and summarized in Table 5. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

TARGET LESIONS

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

NON-TARGET LESIONS

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

NEW LESIONS

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

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each time point. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent time point should be measured from that point on, if the maximum number of measurable new lesions has not been reached. However, for calculation of the sum of diameters for new lesions, iRECIST excludes measurements from new lesions that were not measurable at first appearance.

All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment time point.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥15 mm, it will be considered a measurable new lesion. If at first

appearance the short axis of a lymph node lesion is ≥10 mm and <15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is <10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent time points, even if the short axis decreases to <15 mm (or even <10 mm).

Table 5 Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1
Target lesions	• Measurements should be continued according to RECIST v1.1 conventions.
Non-target lesions	Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (PD), or present without unequivocal progression (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous time point should be evaluated to determine whether there has been any further increase in size.
New lesions	• New lesions should be evaluated for measurability per RECIST v1.1. • All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment time points. • Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each time point. • All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment time point.

Abbreviations: CR=complete response; PD=progressive disease; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.

SUMMARY OF CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

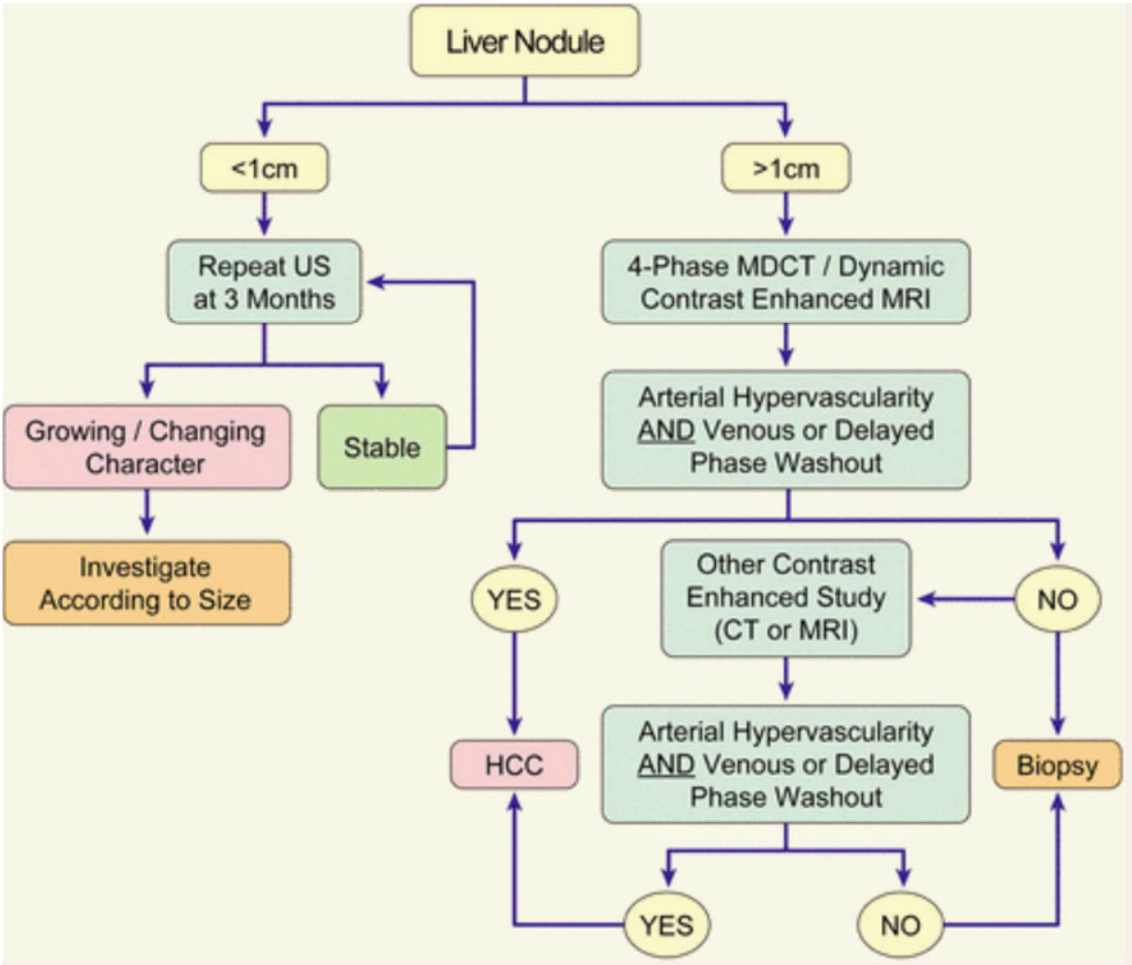
References

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

Seymour L, Bogaerts J, Perrone A, et al. On behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143- e52.

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

Appendix 10
American Association for the Study of Liver Disease (AASLD) Criteria: Algorithm for Investigation of Small Nodules Found on Screening in Patients at Risk for HCC



MDCT=Multi-detector CT scan.

Reference: Bruix J, Sherman M. Management of hepatocellular carcinoma: An Update. Hepatology 2011; 53:1020–22.

Appendix 11
Child-Pugh Classification

Scoring

Measure	Points Scored for Observed Finding		
	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time, [a] seconds over control	1.0–3.0	4.0–6.0	> 6.0
International normalized ratio	< 1.7	1.7–2.3	> 2.3
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Encephalopathy (grade)	None	Mild to moderate (Grade 1 or 2)	Severe (Grade 3 or 4)

*Prolonged time.

Classification

Points	Class
5–6	A
7–9	B
10–15	C

References

Child CG, Turcotte JG. Surgery and portal hypertension. In: The liver and portal hypertension. Edited by Child CG. Philadelphia, Saunders;1964:50-64.

Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus or bleeding oesophageal varices. Br J Surg 1973;60:646-9

Appendix 12
Preexisting Autoimmune Diseases and Immune Deficiencies

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

Table 1 Autoimmune Disease and Immune Deficiencies

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

Appendix 13
Schedule of Activities for Tocilizumab Treatment for Severe or Life-Threatening Cytokine Release Syndrome

Table 1 Schedule of Activities for Tocilizumab Treatment of Severe or Life-Threatening Cytokine Release Syndrome for First Dose

Assessment/Procedure [a]	Pre-Tocilizumab Treatment (within **24 hours** prior)	Tocilizumab Administration	Post-Tocilizumab Treatment[b]						
			0.25 hours	6 hours	1 day	2 days	3 days	8 days	EOTV or EDV
Tocilizumab administration (8 mg/kg for participants at or above 30-kg weight; 12 mg/kg for participants less than 30-kg weight; doses exceeding 800 mg per infusion are not recommended)		X							
Vital signs [c]	x [d]			Measure at least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization [d]					
Pressor documentation [e]	x [d]			Record at least every 6 hours until pressors are discontinued [d]					
FiO2	x [d]			Record at least every 6 hours until participant on room air [d]					
Pulse oximetry, resting	x [d]			Measure at least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization [d]					
Local Laboratory Assessments									
Hematology [f]	x			x	x	x	x	x	
Serum chemistry [g]	x			x	x	x	x	x	
Coagulation (INR, PT, aPTT and fibrinogen)	x			x	x	x	x	x	
Infection workup [h]	x								
Central Laboratory Assessments									
Serum IL-6 PD markers [i]	x		x	x	x	x	x	x	
Serum tocilizumab pharmacokinetics	x		x	x	x	x	x	x	
Tocilizumab ADA	x								x

ADA=Anti-drug antibodies; aPTT=Activated partial thromboplastin time; BUN=blood urea nitrogen; CRP=C-reactive protein; CRS=Cytokine release syndrome; eCRF=Electronic Case Report Form; EDV=Early Discontinuation Visit of study drug (RO7119929); EOTV=End of Treatment Visit of study drug (RO7119929); INR=International normalized ratio; IL-6=interleukin 6; LDH=Lactate dehydrogenase; PD=Pharmacodynamic; PK=Pharmacokinetic; PT=Prothrombin time.

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

[a] Assessments/procedures in this schedule of assessments may be waived by the Medical Monitor if the participant is hospitalized at a facility that does not have the capacity to perform study assessments. Hospitalization should not be prolonged to perform study assessments in this schedule of assessments.

[b] Blood draws for serum tocilizumab PK and serum IL-6 PD markers will be performed post–end of tocilizumab infusion, and will be drawn from the arm which was not used to administer tocilizumab. For post-tocilizumab time points: 0.25 hours, 6 hours, 1 day, 2 days, 3 days and 8 days indicate within 0.25 hours (up to 1 hour), 6 hours ± 30 minutes, 24 ± 4 hours, 48 ± 4 hours, 72 ± 4 hours and 192 ± 4 hours after completion of tocilizumab infusion.

[c] Includes respiratory rate, heart rate, temperature, *oxygen saturation,* and systolic and diastolic blood pressure while the participant is in a seated or supine position, and temperature.

[d] The maximum and minimum values for any 24-hour period should be recorded in the clinical database.

[e] Document vasopressor type and dose in the concomitant medication eCRF if applicable.

[f] Complete blood count including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count.

[g] Includes total and direct bilirubin, AST, ALT, ALP, and lipase. LDH, BUN or urea, creatinine, CRP, calcium, phosphate, glucose, sodium, potassium, bicarbonate, chloride, and serum ferritin.

[h] Includes assessment for bacterial, fungal, and viral infections.

[i] Includes IL-6 and soluble IL-6R.

Table 2 Schedule of Activities for Tocilizumab Treatment of Severe or Life-Threatening Cytokine Release Syndrome for 2nd, 3rd or 4th dose

Assessment/Procedure [a]	Pre-Tocilizumab Treatment (within 24 hours prior)	Tocilizumab Administration	Post-Tocilizumab Treatment[b]		
			0.25 hours	1 day	End of hospitalization
Tocilizumab administration (8 mg/kg for participants at or above 30-kg weight; 12 mg/kg for participants less than 30-kg weight; doses exceeding 800 mg per infusion are not recommended)		x			
Vital signs [c]	x [d]		Measure at least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization [d]		
Pressor documentation [e]	x [d]		Record at least every 6 hours until pressors are discontinued [d]		
FiO2	x [d]		Record at least every 6 hours until participant on room air [d]		
Pulse oximetry, resting	x [d]		Measure at least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization [d]		
Local Laboratory Assessments					
Hematology [f]	x			x	
Serum chemistry [g]	x			x	
Coagulation (INR, PT, aPTT and fibrinogen)	x			x	
Infection workup [h]	x				
Central Laboratory Assessments					
Serum IL-6 PD markers [i]	x		x	x	
Serum tocilizumab pharmacokinetics	x		x	x	

aPTT=Activated partial thromboplastin time; BUN=blood urea nitrogen; CRP=C-reactive protein; eCRF=Electronic Case Report Form; INR=International normalized ratio; IL-6=interleukin 6; LDH=Lactate dehydrogenase; PD=Pharmacodynamic; PK=Pharmacokinetic; PT=Prothrombin time.

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

[a] Assessments/procedures in this schedule of assessments may be waived by the Medical Monitor if the participant is hospitalized at a facility that does not have the capacity to perform study assessments. Hospitalization should not be prolonged to perform study assessments in this schedule of assessments.

[b] Blood draws for serum tocilizumab PK and serum IL-6 PD markers will be performed post–end of tocilizumab infusion, and will be drawn from the arm which was not used to administer tocilizumab. For post-tocilizumab time points: 0.25 hours and 1 day indicate within 0.25 hours (up to 1 hour) and 24 ± 4 hours after completion of tocilizumab infusion.

[c] Includes respiratory rate, heart rate, temperature, *oxygen saturation,* and systolic and diastolic blood pressure while the participant is in a seated or supine position, and temperature.

[d] The maximum and minimum values for any 24-hour period should be recorded in the clinical database.

[e] Document vasopressor type and dose in the concomitant medication eCRF if applicable.

[f] Complete blood count including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count.

[g] Includes total and direct bilirubin, AST, ALT, ALP, and lipase. LDH, BUN or urea, creatinine, CRP, calcium, phosphate, glucose, sodium, potassium, bicarbonate, chloride, and serum ferritin.

[h] Includes assessment for bacterial, fungal, and viral infections.

[i] Includes IL-6 and soluble IL-6R.

Appendix 14
Prognostic Scores for Life Expectancy

Prognostic scores for life expectancy are presented in *Table 1*.

Low risk: 0-1; high risk: 2-3.

Table 1 Prognostic Scores for Life Expectancy

Royal Marsden Hospital Score [a]		Gustave Roussy Immune Score [b]	
Variable	**Score**	**Variable**	**Score**
LDH		**LDH**	
<ULN	0	<ULN	0
>ULN	1	>ULN	1
Albumin, g/L		**Albumin, g/L**	
>35	0	>35	0
<35	1	<35	1
Sites of metastasis		**NLR**	
0-2	0	<6	0
>2	1	>6	1

LDH=Lactate dehydrogenase; NLR=Neutrophil-to-lymphocite ratio; ULN=Upper limit of normal.

[a] Arkenau HT, Barriuso J, Olmos D, et al. Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. J Clin Oncol. 2009;27:2692-96.

[b] Bigot et al. Prospective validation of a prognostic score for patients in immunotherapy phase I trials: the Gustave Roussy Immune Score (GRIm-Score). Eur J Cancer. 2017;84:212-18.