AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A Phase 1/2, open-label, multicenter, dose escalation and dose expansion study of SAR442720 in combination with other agents in participants with advanced malignancies**
Protocol number:	**TCD16210**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR442720**
Study phase:	**Phase 1/2**
Short title:	**Safety and efficacy study of SAR442720 in combination with other agents in advanced malignancies**
Sponsor name:	**Sanofi Research and Development**
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Regulatory agency identifier number(s):

IND:	147102
EudraCT:	2020-000436-22
NCT:	NCT04418661
WHO:	Not applicable
EUDAMED	Not applicable
Other:	Not applicable

Date:	26-Oct-2021	Total number of pages: 178

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	All	26-Oct-2021, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 03	All	29-Mar-2021, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 02	All	02-Jul-2020, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 01	All	06-Mar-2020, version 1 (electronic 3.0)
Original Protocol		27-Jan-2020, version 1 (electronic 1.0)

Amended protocol 04 (26-Oct-2021)

This amended protocol (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of participants, or the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The following changes need to be implemented into the protocol of TCD16210 study:

A new combination cohort with dose escalation and dose expansion parts in participants (NSCLC, KRAS G12C mutant) is to be added. Another cohort of 9 evaluable participants is added to assess the impact of the formulation and the preliminary impact of food on pharmacokinetic(s) of SAR442720 in combination with pembrolizumab. These will result in changes: in the overall study design, schedule of assessments, eligibility criteria, treatment duration, sample size, statistical considerations, and laboratory assessments etc. The safety sections of the protocol are updated in line with the most recent information available.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Study title and short title were updated.	The study title was updated to accommodate the new combination of SAR442720 and adagrasib (MRTX849).
Section 1 (Protocol Summary) and Synopsis	Two new cohorts (Part-3 and Part-4) were added in the study.	Section 1 was updated according to the new information added related to the 2 new cohorts.
Section 1 (Protocol Summary) – Section 1.3	Tables of schedule of activities, PK time points, and pharmacodynamic/biomarker sampling time points were added for Part-3; and a table of PK time point was added for Part-4.	Tables related to the new combination cohort with dose escalation and dose expansion parts and another new cohort to assess the impact of the formulation and the impact of food on PK of SAR442720 in combination with pembrolizumab were added.
Section 2 (Introduction)	Section 2.1 (Study Rationale): The purposes of the Part-3 and Part-4 were added. Section 2.2.2: A new sub-section was added to describe the mechanism of action of adagrasib. Section 2.2.6: A new sub-section was added to describe the rationale for combining SAR442720 with adagrasib Section 2.3: The benefit/risk assessment section was updated as per the new adagrasib combination. Section 2.3.1.1 (Potential risks of SAR442720): This section was updated according to the new information added in the most recent Investigator's Brochure (IB). Section 2.3.1.2 (Potential risks of pembrolizumab): This section was updated according to the new information added in the most recent USPI. Section 2.3.1.2 (Potential risks of SAR442720 and pembrolizumab administration): This section was updated according to the most recent IB. Section 2.3.1.4 and 2.3.1.5: New subsections were added to describe the potential risks of adagrasib and its combination with SAR442720. Section 2.3.3: Details of Study 849-001 of adagrasib were added. Section 2.3.4: The benefit and risk conclusion statement was updated as per the combination of SAR442720 and adagrasib.	The overall introduction section was updated according to the requirements of Part-3 and Part-4 of the study, and the sections related to SAR442720 and pembrolizumab were updated according to new information available in the most recent IB and USPI, respectively.

Section # and Name	Description of Change	Brief Rationale
Section 3 (Objectives And Endpoints)	Part-3 and Part-4 related objectives and endpoints were added to the table. Disease control rate (DCR) is also added as a secondary endpoint to assess anti-tumor activity in Part-2 as mentioned in Part-3B of the study.	The overall study objectives and endpoints were adjusted to accommodate Part-3 and Part-4 of the study. DCR is also added as an endpoint in Part-2, in alignment with Part-3B of the study.
Section 4 (Study Design)	Study design was updated for Part-3 and Part-4 of the study. Minor consistency related edits were made in the text for Part-2 study design in context to the respective SoA table (Section 1.3) of the study. Section 4.1.1 (Dose-limiting toxicity criteria): This section was updated to accommodate the requirements of Part-3A of the study. Section 4.1.2 (Dose escalation): This section was updated to accommodate the requirements of Part-3 of the study. Section 4.2: The scientific rationale of the study design was updated for Part-3 and Part-4 of the study. Section 4.3: The justification for dose was updated for Part-3 and Part-4 of the study.	The overall study design section was updated as per the addition of Part-3 and Part-4 of the study. Part-2 text updated for consistency with the respective SoA table.
Section 5 (Study Population)	Section 5.1 (Inclusion Criteria): Inclusion criteria, I01, I02, I03, I04, I05, I06, I07, and I09 were updated to differentiate which criteria belong to which part of the study and I12, and I13 for Part-3 were added. Section 5.2 (Exclusion Criteria): E07 was updated to 'medically controlled atrial fibrillation >6 month'; Exclusion criteria, E08 and E10 were updated to differentiate which criteria belong to which part of the study; E11 was updated to included "active pneumonitis" and "radiation pneumonitis that required steroids is not permitted"; E13 updated with hepatitis-C virus; E14 updated to include ductal carcinoma in situ of the breast carcinoma as an exception; E22, E29, E30, and E31 for Part-3 were updated/added.	Inclusion and exclusion criteria of the study were updated as per the study requirements and the addition of Part-3.
Section 5.3.1 (Meals and Dietary Restrictions)	Instructions for meal consumption for Part-3 and Part-4 participants were added.	The instructions were updated for Part-3 and Part-4 participants.
Section 6 (Study Intervention)	Details of the new tablet formulation were added in Table 16. Table 17, a new table with details of adagrasib used as a new combination intervention in Part-3 of the study was added. Section 6.1.1 (Investigational medicinal product): the details of adagrasib for Part-3 added of the study were. Section 6.2: Adagrasib preparation/handling/storage details were added.	The new study intervention of adagrasib was added for Part-3 and the tablet formulation was added for Part-4. Updates were made for the Part-3 combination.

Section # and Name	Description of Change	Brief Rationale
Section 6.4 (Study intervention compliance)	Details of study intervention compliance updated for Part-3 and Part-4 of the study.	Updates were made for the Part-3 and Part-4 of the study.
Section 6.4.1 (Missed Dose)	Instructions were added for participants if they missed any dose of adagrasib.	Updates were made for the for Part-3 combination.
Section 6.5.1 (Prohibited Concomitant Therapy)	Details of the drugs that are prohibited while taking adagrasib were added along with exceptions for Part-3 of the study.	Updates were made for the for Part-3 combination.
Section 6.6 (Dose Modification)	Dose modification and event management details for Part-3 and Part-4 were added throughout the section.	The overall section was updated for Part-3 and Part-4.
Section 6.7 (Intervention After the End of the Study)	Details related to study intervention of SAR442720 and pembrolizumab to be received by the participants were updated.	This information was clarified
Section 7.1 (Discontinuation of Study Intervention)	Details of adagrasib added.	This section updated as per Part-3 of the study.
Section 8 (Study Assessments And Procedures)	Section 8.1, Efficacy Assessments: Assessments for Part-3A and Part-4 were added.	Efficacy assessments were updated according to the new Part-3A and Part-4 of the study.
Section 8.3.6 (Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs)	Section 8.3.6, was deleted.	This was a correction; this section was not applicable to oncology studies.
Section 8.3.7 (Adverse event of special interest)	Section 8.3.7 previously, now as Section 8.3.6, This section was updated with the details of adagrasib overdose.	Updated for the Part-3 combination drug.
Section 8.5 (Pharmacokinetics)	Standard text in the section was updated as per the new template along with the details for Part-3 and Part-4 of the study.	Updated per the new Sanofi protocol template and as per the Part-3 and Part-4 of the study.
Section 8.6 (Pharmacodynamics)	Details of Part-3 and Part-4 were added, and the section was updated according to the study requirements.	Updated as per the Part-3 and Part-4 cohorts.
Section 8.7 (Genetics)	Standard text about genetics analyses from Section 8.5 was moved to this section as per the new template	Updated per the new Sanofi protocol template.
Section 8.8: (Biomarkers)	The language in this section was updated for better presentation.	Updated for the Part-3 combination.
Section 8.9: (Immunogenicity Assessments)	Details of adagrasib were added.	Updated to clarify applicable parts of the study.
Section 9 (Statistical Considerations)	The statistical hypothesis, sample size determination and population, general consideration, and efficacy and safety endpoints sections were updated	Statistical considerations were updated according to the new Part-3 and Part-4 of the study.
Section 10.2 (Appendix 2)	Table 22, Protocol-required laboratory assessments updated.	Updated as per the study requirements.

Section # and Name	Description of Change	Brief Rationale
Section 10.3 (Appendix 3)	Definition of AE was updated.	Correction of the language used for the oncology study.
Section 10.4 (Appendix 4)	Duration for using any contraception measures (male/female) is updated from 4 months to 6 months.	Contraceptive guidance updated as per other similar study protocols.
Section 10.5 (appendix 5)	Tenure of genetic sample retention was updated from 10 years to 15 years.	Updated to be consistent with the Sponsor's other study protocols.
Section 10.9 (Appendix 9)	Dose modification guidelines for SAR442720 and adagrasib combination were added.	Updated for the Part-3 combination.
Section 101.10 (Appendix 10)	List of prohibited medications updated as per adagrasib addition in Part-3.	Updated for the Part-3 combination.
Section 10.11 (Appendix 11)	Dose escalations details for Part-3 were added.	Updated for the Part-3 combination.
Section 10.13 (Appendix 13)	A new appendix for 'menus and composition for food effect study' was added.	Two tables (diet plan) were added for non-vegan and vegan participants in the new Part-4 of the study.
Section 11 (Reference)	Section 11 was updated with new references.	Updated to account for the new citations added.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A Phase 1/2, open-label, multicenter, dose escalation and dose expansion study of SAR442720 in combination with other agents in participants with advanced malignancies.

Short title: Safety and efficacy study of SAR442720 in combination with other agents in advanced malignancies

Rationale:

SAR442720 (also known as RMC-4630) is a potent, selective, and orally bioavailable Src Homology region 2 domain−containing protein tyrosine phosphatase 2 (SHP2) allosteric inhibitor. SHP2 is a positive regulator of RAS activation. SHP2 is also involved in signaling in T-cells. It binds with programmed cell death protein 1 (PD-1) following programmed death-ligand 1 (PD-L1) stimulation and inhibits T cell activation. Therefore, targeting SHP2 may restore or even enhance T-cell functions. The costimulatory receptor CD-28, and to some extent the T-cell receptor, are dephosphorylated and de-activate some critical components of the interferon gamma (IFNγ) signaling cascade. Defects in this cascade have been described as a key component of resistance to anti-PD1 therapy. SHP2 inhibition may increase the efficacy of PD1 inhibitors in patients with high PD-L1 expression but may also sensitize patients with low PD-L1 expression to a PD1 inhibitor (1, 2).

Immune Checkpoint Inhibitor (ICI) in combination with standard of care (SoC) chemotherapy/platinum doublet has significantly improved overall survival (OS) in non-small cell lung cancer (NSCLC). In dose escalation (Part-1), the aim of this study is to evaluate the safety, maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of SAR442720 in combination with ICI, pembrolizumab, in participants with solid tumors including advanced/metastatic NSCLC or colorectal cancer (CRC). In addition, expansion part (Part-2) of the study seeks preliminary clinical efficacy of SAR442720 in combination with pembrolizumab in participants with advanced solid tumors.

As a positive downstream regulator of receptor tyrosine kinases and upstream regulator of RAS activation, SHP2 is an important target for tumors with active RAS cycling. The RAS family of oncogenes is frequently activated by mutations in human cancers, while KRAS G12C is the most frequent mutation in lung cancer. Targeted inhibition of the KRAS G12C mutation has been shown to be clinically effective for this previously intractable cancer (3, 4). Part-3 of this study will evaluate the safety, recommended Phase 2 dose (RP2D) and anti-tumor effect of SAR442720 in combination with a KRAS G12C inhibitor, adagrasib (MRTX849), in participants with advanced NSCLC and KRAS G12C mutation.

To evaluate the effect of food on the pharmacokinetic(s) (PK) of SAR442720 tablet and to assess the relative bioavailability of SAR442720 tablet formulation (test) compared to the SAR442720 capsule formulation (reference) when dosed in combination with pembrolizumab in participants with advanced malignancies, the Sponsor is conducting Part-4 of the study.

Part-1 Dose Escalation (SAR442720 and pembrolizumab)

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of SAR442720 in combination with pembrolizumab in participants with advanced solid tumors including non-small cell lung cancer (NSCLC) who progressed on anti-PD1/PD-L1 containing therapy and advanced CRC after progression to all standard of care (SoC) therapy.	• Incidence, nature, and severity of treatment-emergent adverse events (AEs) and serious adverse events (SAEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 for the combination of SAR442720 and pembrolizumab.
• To define the MTD and RP2D for the combination of SAR442720 and pembrolizumab in participants with solid tumors.	• Incidence of study drug-related dose limiting toxicities (DLTs) in Cycle 1.
Secondary	
• To assess the pharmacokinetic(s) (PK) of SAR442720 in combination with pembrolizumab, and to assess the PK of pembrolizumab in combination with SAR442720.	• **Plasma concentrations of SAR442720** • Serum concentrations of pembrolizumab
• To estimate the anti-tumor effects of SAR442720 in combination with pembrolizumab in all participants.	• Objective response rate (ORR) and duration of response (DoR) of SAR442720 and pembrolizumab in all participants. ORR of combination therapy with SAR442720 and pembrolizumab will be based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Part-2 Dose Expansion (SAR442720 and pembrolizumab)

Objectives	Endpoints
Primary	
• To determine the anti-tumor activity of SAR442720 in combination with pembrolizumab.	• Objective response rate defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR) determined by the Investigator, per RECIST v1.1
Secondary	
• To assess the safety profile of SAR442720 in combination with pembrolizumab.	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.
• To assess other indicators of anti-tumor activity.	• Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first documented evidence of PR or CR determined by the Investigator per RECIST v1.1 (for NSCLC). • DoR, defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined by the Investigator per RECIST v1.1 or death from any cause, whichever occurs first.

Objectives	Endpoints
	• Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months determined by the Investigator per RECIST v1.1. • Disease control rate (DCR) including confirmed CR or PR or SD as determined by the Investigator per RECIST v1.1. • Progression free survival (PFS), defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by the Investigator as per RECIST v1.1 or death due to any cause, whichever occurs first.
• To assess the PK of SAR442720 in combination with pembrolizumab, and to assess the PK of pembrolizumab in combination with SAR442720.	• Plasma concentrations of SAR442720. • Serum concentration of pembrolizumab.

Part-3A Dose Escalation (SAR442720 and adagrasib)

Objectives	Endpoints
Primary	
• To define the MTD and RP2D for the combination of SAR442720 and adagrasib in participants with NSCLC and KRAS G12C mutation.	• Incidence of study drug-related DLTs in Cycle 1.
• To characterize the safety and tolerability of SAR442720 in combination with adagrasib in participants with NSCLC and KRAS G12C mutation.	• Incidence, nature, and severity of TEAEs and SAEs graded according to NCI CTCAE v5.0 for the combination of SAR442720 and adagrasib.
Secondary	
• To characterize the PK of SAR442720 in combination with adagrasib, and to characterize the PK of adagrasib in combination with SAR442720.	• PK parameters of SAR442720 (C_{max}, T_{max}, $AUC_{0\text{-}last}$). • PK parameters of adagrasib (C_{max}, T_{max}, $AUC_{0\text{-}last}$).
• To estimate the anti-tumor effects of SAR442720 in combination with adagrasib in all participants.	• ORR and DoR of SAR442720 and adagrasib in all participants. ORR of combination therapy with SAR442720 and adagrasib will be based on RECIST v1.1.

Part-3B Dose Expansion (SAR442720 and adagrasib)

Objectives	Endpoints
Primary	
• To determine the anti-tumor activity of SAR442720 in combination with adagrasib in participants with NSCLC and KRAS G12C mutation.	• ORR defined as the proportion of participants who have a confirmed CR or PR determined by the Investigator per RECIST v1.1.
Secondary	
Objectives	**Endpoints**
• To assess the safety profile of SAR442720 when combined with adagrasib in participants with NSCLC and KRAS G12C mutation.	• Incidence of TEAEs, SAEs, and laboratory abnormalities according to NCI CTCAE v5.0.

Objectives	Endpoints
• To assess other indicators of anti-tumor activity.	• TTR defined as the time from the first administration of investigational medicinal product (IMP) to the first documented evidence of PR or CR determined by the Investigator per RECIST 1.1 (for NSCLC). • DoR, defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined by the Investigator per RECIST 1.1 or death from any cause, whichever occurs first. • CBR including confirmed CR or PR at any time or SD of at least 6 months (determined by the Investigator per RECIST v1.1. • DCR including confirmed CR or PR or SD as determined by the Investigator per RECIST v1.1. • PFS, defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by the Investigator as per RECIST v1.1 or death due to any cause, whichever occurs first.
• To assess the PK of SAR442720 in combination with adagrasib, and to assess the PK of adagrasib in combination with SAR442720.	• Plasma concentrations of SAR442720 and adagrasib.

Part-4 (SAR442720 and pembrolizumab)

Objectives	Endpoints
Primary	
• To evaluate the impact of food on the PK of SAR442720 when dosed in combination with pembrolizumab.	• Plasma PK parameters of SAR442720 following oral administration of SA442720 tablets in combination with pembrolizumab under fed and fasted states (eg. C_{max}, T_{max}, $AUC_{0\text{-}last}$).
• To evaluate the impact of the formulation (tablets vs. capsules) on the PK of SAR442720 when dosed in combination with pembrolizumab.	• Plasma PK parameters of SAR442720 following oral administration of SAR442720 tablets (test formulation) and capsules (reference formulation) in combination with pembrolizumab under fasted state (eg, C_{max}, T_{max}, $AUC_{0\text{-}last}$).
Secondary	
• To assess the safety and tolerability of SAR442720 under fasted and fed conditions in combination with pembrolizumab through the cycles, when dosing with capsule and tablet formulations in combination with pembrolizumab. • To estimate the anti-tumor effects of SAR442720 in combination with pembrolizumab in all participants.	• Incidence, nature, and severity of TEAEs and SAEs, graded according to the NCI CTCAE v5.0 for SAR442720 in combination with pembrolizumab • ORR and DoR of SAR442720 and pembrolizumab in all participants. ORR of combination therapy with SAR442720 and pembrolizumab will be based on RECIST v1.1.

Overall design:

This is a Phase 1/2 open-label, multi-center, safety, preliminary efficacy, and PK study of SAR442720 in combination with other agents in participants with advanced malignancies.

Part-1 of the study is to characterize the safety and tolerability of SAR442720 in combination with pembrolizumab and to confirm the RP2D. Participants with either NSCLC or advanced CRC will be enrolled in the study.

SAR442720 will be administered orally on a continuous basis. The starting dose (DL1) of SAR442720 is 140 mg Day 1 and Day 4 twice weekly (BIW) with pembrolizumab given at 200 mg intravenous (IV) once every 3 weeks (Q3W). During the study, alternative BIW dose schedules, such as Day 1 and Day 2 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study can be explored after agreement of the Study Committee. The dose of SAR442720 will be escalated or de-escalated depending on the emerging safety data of the combination. [redacted]One of the BIW dose schedules will be tested, based on the safety and tolerability data from the ongoing Phase 1 monotherapy escalation study. The decision to initiate alternative dose levels will be made by the Study Committee after careful evaluation of safety and/or PK data from the ongoing Phase 1 monotherapy escalation study and data generated in this combination study. Overall safety monitoring will be performed throughout the conduct of the study. Additional dose levels and/or additional schedules of administration could be tested based on emerging PK and safety data.

The DLT () observation period is 1 cycle (21 days). All the adverse events (AEs) occurring during treatment, unless due to disease progression or to a cause obviously unrelated to investigational medicinal product (IMP), will be taken into consideration by the Sponsor and recruiting Investigators for the determination of the MTD and RP2D for the SAR442720 and pembrolizumab combination. The Study Committee will review the overall safety, PK/PDy and activity data and in agreement with the Sponsor's Study Medical Manager will decide the recommended dose for the expansion phase.

The Study Committee will be comprised of the Principal Investigator from each site involved in the dose escalation phase, clinical team members from the Sponsor (including at least the Study Medical Manager, Global Study Manager, and experts when appropriate such as Global Safety Officer, pharmacokineticists, biostatisticians).

The Study Committee will review clinical data on a regular basis, with a review being performed at least at the end of each DL cohort, before the enrollment of new participants at the next DL, and at the end of the dose escalation phase of the study. The Study Committee in agreement with the Sponsor's Study Medical Manager will decide on whether to escalate or de-escalate to the next DL or to add alternative dose levels during Study Committee meetings based on current safety profile and tolerability, available PK information, and statistical design recommendation. Decisions regarding participant treatment and cohort expansion will be discussed and clearly documented in the discussion minutes. The Study Committee in agreement with the Sponsor's

Study Medical Manager may permit the evaluation of additional DL and/or additional schedules of administration of SAR442720, depending upon the observed safety and DLT at each DL, and the safety and/or PK data observed in the ongoing Phase 1 monotherapy escalation study.

Table 1 - Dose escalation for Part-1

Dose Level (DL)	SAR442720	Pembrolizumab
DL1	140 mg BIW	200 mg Q3W
DL2	200 mg BIW	200 mg Q3W
DL-1	100 mg BIW	200 mg Q3W

BIW = Day 1 and Day 2 of each week, Day 1 and Day 4 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study; Q3W = once every 3 weeks

The National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE Version 5.0 will be used to assess the severity of AEs. Causal relationships are to be determined by the Investigator. The potential DLTs will be confirmed by the Sponsor and recruiting Investigators.

Part-2

The expansion cohort (Part-2), un-controlled, non-randomized, open-label will assess the anti-tumor activity and safety of SAR442720 combined with pembrolizumab in participants with NSCLC.

Part-2 will assess the anti-tumor efficacy and safety of adding SAR442720 to pembrolizumab as 1L NSCLC therapy.

- Cohort A1: participants with PD-L1 tumor proportion score (TPS) ≥50% NSCLC to receive SAR442720 + pembrolizumab as 1L therapy.
- Cohort A2: participants with PD-L1 TPS 1%-49% NSCLC to receive SAR442720 + pembrolizumab as 1L therapy.

Part-2 of the study will start once RP2D for SAR442720 from Part-1 is confirmed. The SAR442720 dose will be 200 mg BIW, Day 1 and Day 2 of each week, administered orally (21 days per cycle). This dose emerged as the safe dose of SAR442720 from the escalation part (Part-1) of this study. Pembrolizumab will be administered as a dose of 200 mg using a 30 minutes IV infusion on Day 1 every 3 weeks (21 days cycle) or a dose of 400 mg using 30 minutes IV infusion on Day 1 and every 6 weeks (42 days cycle).

Part-3

Part-3 of this open-label, multi-center, un-controlled, non-randomized study, will assess the safety, (RP2D, anti-tumor activity, and PK of SAR442720 in combination with adagrasib in participants with NSCLC harboring KRAS G12C mutation.

Part-3A

SAR442720 and adagrasib will be administered orally on a continuous basis. The starting dose (DL1) of SAR442720 will be 100 mg on Day 1 and Day 2 BIW with adagrasib given at 400 mg twice daily (BID) orally. The dose escalation will follow the modified toxicity probability interval 2 (mTPI2) design with a minimum of 3 participants evaluable for DLT for each dose level. Participants will be DLT-evaluable if they have taken at least 80% of the scheduled Cycle 1 dose of both drugs in the first 21 days of treatment. The same mTPI-2 design as that used in Part-1 will be used in Part-3A.

The dose of SAR442720 will be escalated or de-escalated depending on the emerging safety data of the combination. The starting dose (DL1) of SAR442720 will be 100 mg BIW, which is 50% of the highest cleared dose in the ongoing Phase 1 monotherapy dose escalation study (https://clinicaltrials.gov; NCT03634982). Dose Level 2 (DL2) (140 mg BIW) and dose level 3 (DL3) (200 mg BIW) for SAR442720 have been cleared in the ongoing Phase 1 monotherapy dose escalation study. The adagrasib starting dose (DL1) will be 400 mg BID orally, which is 1 dose level below the RP2D in monotherapy (3). The design of the study assumes 5 combination dose levels with 3 to 6 participants per dose level. At least 6 participants need to be treated at the MTD and RP2D. In Part-3A approximately 15 to 30 DLT-evaluable participants are expected to be enrolled during the dose escalation part.

Part-3B

The Part-3B dose expansion will assess the anti-tumor activity and safety of SAR442720 combined with adagrasib in participants with NSCLC harboring KRAS G12C mutation.

The Part-3B dose expansion of the study will start once RP2D for SAR442720 and adagrasib from the Part-3A dose escalation is confirmed.

Approximately 40 participants will be enrolled in Part-3B dose expansion and treated at the RP2D identified in Part-3A.

Part-4

The Part-4 of this Phase 1/2, open-label, multi-center, non-randomized study will assess the effect of food on the PK of SAR442720 tablet, when dosed in combination with pembrolizumab in participants with advanced malignancies. It will also evaluate the relative bioavailability of SAR442720 tablet formulation (test) compared to the SAR442720 capsule formulation (reference) when dosed in combination with pembrolizumab in participants with advanced malignancies.

SAR442720 and pembrolizumab will be administered on a continuous basis, with SAR442720 administered orally at the RP2D determined from Part-1, and pembrolizumab administered intravenously at 200 mg Q3W or 400 mg Q6W. The SAR442720 tablet formulation (test) will be administered during the first cycle (21 days), and starting from C2D1, SAR442720 capsule formulation (reference) will be administered until the end of treatment (EOT). On C1D1, each participant will receive SAR442720 tablet in combination with pembrolizumab with a moderate-calorie moderate-fat breakfast after an overnight fast of 10 hours. The breakfast should be consumed within 0.5 hour, and there should be another 4 hour fast after the completion of breakfast. On C1D15, each participant will receive SAR442720 tablet after a 10 hour overnight fast prior to dosing on C1D15, followed by a 4 hour fast postdose. On C2D1, each participant will receive SAR442720 capsule in combination with pembrolizumab after a 10 hour overnight fast prior to dosing on C2D1, followed by a 4 hour fast postdose. For all other days (except for C1D1, C1D15, and C2D1), participants will be fasted for 1 hour prior and 1 hour after each SAR442720 dose. Water will be permitted ad lib for participants in either fasted or fed state, except for 1 hour before and 1 hour after the administration of SAR442720. Participants will be instructed to take SAR442720 with 240 mL of water.

Disclosure Statement: This is a non-randomized study with SAR442720 in combination with other agents (pembrolizumab or adagrasib) with no masking in participants with advanced malignancies.

Number of participants:

Approximately 18 to 24 DLT evaluable participants are expected to be enrolled during the Dose Escalation and mini-expansion cohort (Part-1). It assumes 3 combination dose levels (as shown above) with 3 to 6 participants per dose level. At least 6 participants need to be treated at the MTD. After the MTD is identified, another 6 participants will be treated at the MTD to confirm the decision and determine the RP2D. The actual sample size will vary depending on DLTs observed and the number of dose levels explored.

In Part-2 approximately 40 participants will be enrolled and treated at RP2D determined from Part-1. It is planned to enroll 20 participants with PD-L1 TPS ≥50% (Cohort A1) and 20 participants with PD-L1 TPS in 1-49% (Cohort A2).

In Part-3A, approximately 15-30 DLT evaluable participants are expected to be enrolled. In Part-3B, approximately 40 participants at the RP2D determined from Part-3A will be enrolled.

In Part-4, up to approximately 12 participants will be enrolled.

“Note: Enrolled participants are all participants from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not”.

Intervention groups and study duration:

Part-1 and Part-4

The duration of the study for a participant will include a period for screening of up to 28 days. Participants will be evaluated for safety and tolerability. Once successfully screened, enrolled participants may receive study intervention until disease progression, unacceptable AE, or the participant's or investigator's decision to stop the treatment. Each cycle of treatment will have duration of 21 days. After discontinuing study intervention, participants will return to the study site approximately 30 days after the last IMP administration or before the participant receives another anti-cancer therapy, whichever is earlier, for end-of-treatment assessments. Participants without documented disease progression at the end of a treatment visit who have not yet started treatment with another anti-cancer therapy will proceed with 3 months follow-up visits until initiation of another anti-cancer therapy, disease progression, death, or study cutoff date (whichever comes first). The expected duration of study intervention for participants may vary, based on progression date; median expected duration of study per participant is estimated to be 10 months (up to 1 month for screening, a median of 6 months for treatment, and a median of 3 months for long term follow-up).

Part-2 and Part-3

The duration of the study for a participant will include:

- Screening period: up to 28 days.
- Treatment Period: enrolled participants will receive continuous treatment until PD, unacceptable AE, and other full permanent discontinuation criteria as described in Section 7.1.
- End of treatment and Follow-up: EOT visit will occur 30 days ±5 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the follow up (not applicable to Part-3) and will be followed differently depending on the reason leading to EOT:
    - Participants who discontinue study treatment with radiological or clinical progressive disease (PD) (per [Response Evaluation Criteria in Solid Tumors (RECIST)] v1.1) or iCPD (per iRECIST) will be followed in the Follow-Up Visit 1 occurring 3 months ±5 days from last IMP administration, or until start of new anticancer therapy or cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.

For Part-2 and Part-3B, the primary endpoint (objective response rate [ORR]) analyses is performed when all participants have at least 2 post baseline tumor assessments with response durability demonstrated or discontinue study treatment (whichever occurs first).

Study intervention(s)

Investigational medicinal products

SAR442720 capsules

- Formulation: SAR442720 capsules are supplied as powder-in-capsule drug products of 20 mg and 100 mg. The capsules are packaged in high-density polyethylene (HDPE) bottles.
- Route of administration: Oral with water after 1 hour fast; no food or drink (other than water) allowed for 1 hour after administration (C1D1, C1D15 and C2D1 in Part-4 are exceptions).
- Dose regimen: SAR442720 capsules will be administered orally BIW (Day 1 and Day 2 of each week or, Day 1 and Day 4 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study). The starting dose is 140 mg on Day 1 and Day 4 each week in Part-1 and 100 mg BIW, Day 1 and Day 2 in Part-3A. The dosing regimen of Part-2 and Part-4 is 200 mg on Day 1 and Day 2 BIW.

SAR442720 tablets

- Formulation: SAR442720 tablets are supplied as film-coated tablets drug products of 20 mg and 100 mg. The tablets are packaged in Aclar blisters containing 8 tablets.
- Route of administration: Oral with water after 1 hour fast; no food or drink (other than water) is allowed for 1 hour after administration (C1D1, C1D15, and C2D1 in Part-4 are exceptions).
- Dose regimen: SAR442720 tablets will be administered orally BIW (Day 1 and Day 2 of each week or, Day 1 and Day 4 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study). The dosing regimen of Part-4 is 200 mg on Day 1 and Day 2 BIW.

Pembrolizumab

- Formulation: 50 mg lyophilized powder in single-dose vial for reconstitution or 100 mg/4 mL (25 mg/mL) solution in a single-dose vial
- Route of administration: IV infusion
- Dose regimen: Pembrolizumab will be administered at 200 mg via IV infusion over 30 minutes Q3W or 400 mg via IV infusion over 30 minutes Q6W (for Part-2 and Part-4) in accordance with the label as mentioned in Section 6.1.1.

Adagrasib (Part-3 only)

- Formulation: MRTX849 is supplied as immediate release film-coated tablets of 200 mg. The tablets are packaged in HDPE bottles.
- Route of administration: Oral with at least 240 mL (8 ounces) of water; may be taken with or without food. When co-administered with SAR442720, adagrasib should be taken without food (as SAR442720).
- Dose regimen: Adagrasib will be administered orally BID (two times a day) each day. The starting dose is 400 mg BID each day; this should be at 12-hour intervals to the extent possible.

Statistical considerations:

Part-1

- **Primary endpoint:** The primary endpoints in the Part-1 are incidence, nature, and severity of DLTs, AEs, and SAEs. The treatment-emergent adverse event (TEAE) period is defined as the time from the first dose of study interventions up to 30 days after last dose of study interventions. The number and percentage of participants experiencing TEAEs by primary system organ class and preferred term (PT) will be summarized by NCI CTCAE Version 5.0 grade (all grades and Grade ≥3). Similar tables will be prepared for treatment-related TEAEs, adverse event of special interest (AESIs), TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, delay or omission, serious TEAEs and TEAEs with fatal outcome.
- **Main secondary endpoints:** Secondary endpoints include laboratory results, ORR, duration of response (DoR), and PK concentrations.

  Clinical laboratory test results will be graded according to NCI CTCAE Version 5.0, when applicable. Number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the TEAE period will be provided for all-treated population.

  The ORR per RECIST v1.1 will be summarized with descriptive statistics with a 90% 2-sided confidence interval (CI). DoR will be analyzed using Kaplan-Meier method.

  PK concentrations of SAR442720 and pembrolizumab will be summarized with descriptive statistics.

Part-2

- **Primary endpoint:** The primary endpoint in the Part-2 is ORR. The ORR per RECIST v1.1 will be summarized with descriptive statistics with a 90% 2-sided CI.
- **Main secondary endpoints:** Secondary endpoints include AEs, laboratory results, DoR, progression free survival (PFS), time to response (TTR) and clinical benefit rate (CBR), disease control rate (DCR), and PK concentrations.

  Incidence and severity of AEs and SAEs will be summarized. The number and percentage of participants experiencing TEAEs by primary system organ class and PT will be summarized by NCI CTCAE Version 5.0 grade (all grades and Grade ≥3). Similar tables

will be prepared for treatment-related TEAEs, adverse event of special interest (AESIs), TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, delay or omission, serious TEAEs and TEAEs with fatal outcome.

Clinical laboratory test results will be graded according to NCI CTCAE Version 5.0, when applicable. Number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the TEAE period will be provided for all-treated population.

The DoR and PFS will be analyzed using Kaplan-Meier method.

The PK concentrations of SAR442720 and pembrolizumab will be summarized with descriptive statistics.

Part-3A

- **Primary endpoint:** The primary endpoints in the Part-3A are incidence, nature, and severity of DLTs, AEs, and SAEs. The TEAE period is defined as the time from the first dose of study interventions up to 30 days after last dose of study interventions. The number and percentage of participants experiencing TEAEs by primary system organ class and PT will be summarized by NCI CTCAE Version 5.0 grade (all grades and Grade ≥3). Similar tables will be prepared for treatment-related TEAEs, AESIs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, delay or omission, serious TEAEs and TEAEs with fatal outcome.
- **Main secondary endpoints:** The secondary endpoints include laboratory results, ORR, DoR, PFS, TTR, CBR, and PK.

  Clinical laboratory test results will be graded according to NCI CTCAE Version 5.0, when applicable. Number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the TEAE period will be provided for all-treated population.

  The DoR and PFS will be analyzed using Kaplan-Meier method.

  The PK parameters of SAR442720 and adagrasib will be summarized with descriptive statistics.

Part-3B

- **Primary endpoint:** The primary endpoint in Part-3B is ORR. The ORR per RECIST v1.1 will be summarized with descriptive statistics with a 90% 2-sided CI.
- **Main secondary endpoints:** The secondary endpoints include AEs, laboratory results, DoR, PFS, TTR CBR, DCR, and PK.

  The incidence and severity of AEs and SAEs will be summarized. The number and percentage of participants experiencing TEAEs by primary system organ class and PT will be summarized by NCI CTCAE Version 5.0 grade (all grades and Grade ≥3). Similar tables will be prepared for treatment-related TEAEs, AESIs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, delay or omission, serious TEAEs, and TEAEs with fatal outcome.

Clinical laboratory test results will be graded according to NCI CTCAE Version 5.0, when applicable. Number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the TEAE period will be provided for the all-treated population.

The DoR and PFS will be analyzed using Kaplan-Meier method.

The PK concentrations of SAR442720 and adagrasib will be summarized with descriptive statistics.

Part-4

- **Primary endpoint**: The PK parameters of SAR442720 will be estimated with non-compartmental analysis and summarized using descriptive statistics. The geometric mean ratios and 90% confidence intervals of AUC and C_{max} will be computed for SAR442720 between fed and fasted states of tablet formulation (C1D1 to C1D15) and between the tablet (test) and capsule (reference) formulations (C1D15 to C2D1). In addition, the PK parameters in Part-4 will be analyzed using a mixed effect model, which will be provided in SAP.
- **Secondary endpoints**: The secondary endpoints include AEs, ORR, and DoR.

  The incidence and severity of AEs and SAEs will be summarized. The number and percentage of participants experiencing TEAEs by primary system organ class and PT will be summarized by NCI CTCAE Version 5.0 grade (all grades and Grade ≥3). Similar tables will be prepared for treatment-related TEAEs, AESIs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, delay or omission, serious TEAEs, and TEAEs with fatal outcome.

  The ORR per RECIST v1.1 will be summarized with descriptive statistics with a 90% 2-sided confidence interval.

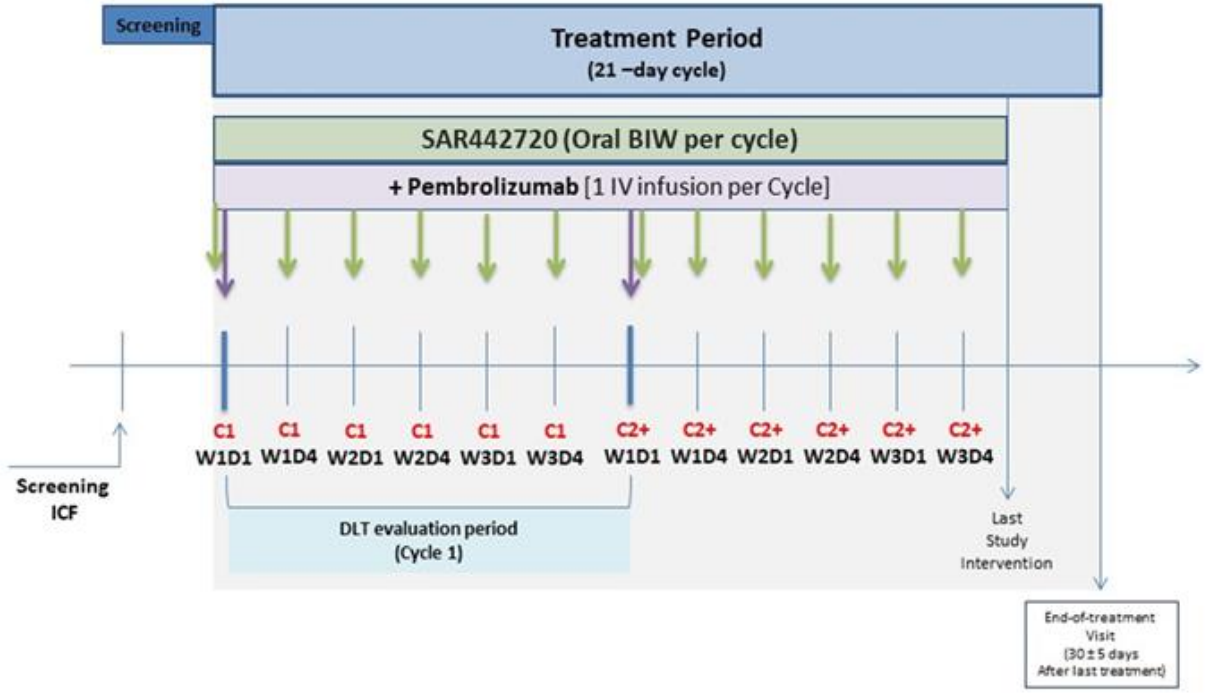
  The DoR will be analyzed using the Kaplan-Meier method.

Data Monitoring Committee:

No DMC was appointed.

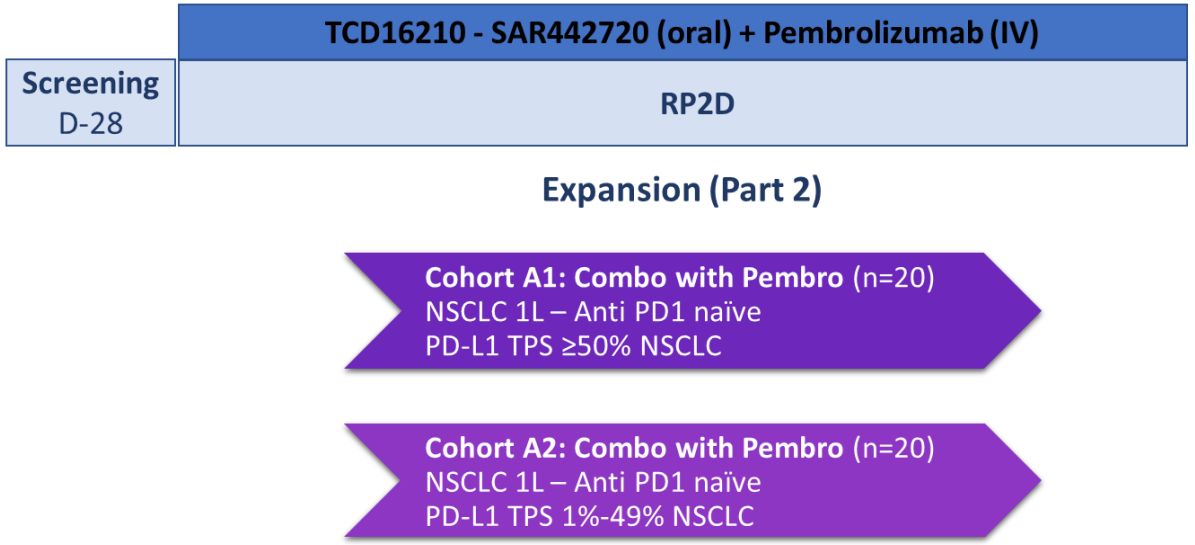
1.2 SCHEMA

Figure 1 - Graphical study design of SAR442720 administered BIW and pembrolizumab every 3 weeks for Part-1



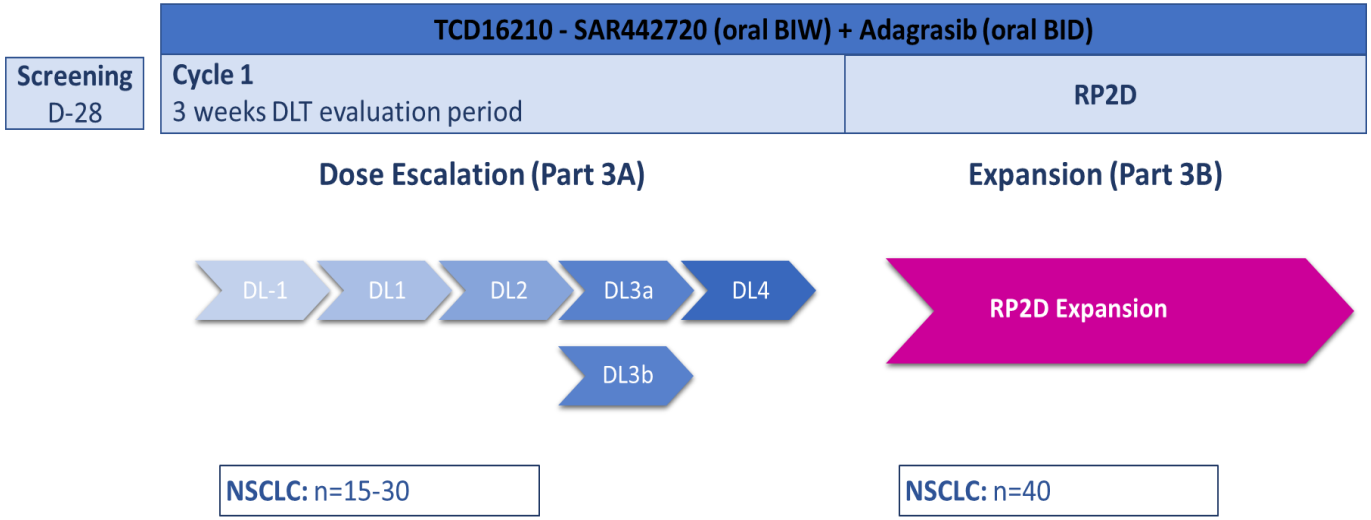
Abbreviations: BIW = twice a week, C = Cycle, D = Day; DLT = dose-limiting toxicities, ICF = informed consent form, W = Week.

Figure 2 - Graphical study design of SAR442720 and pembrolizumab for Part-2



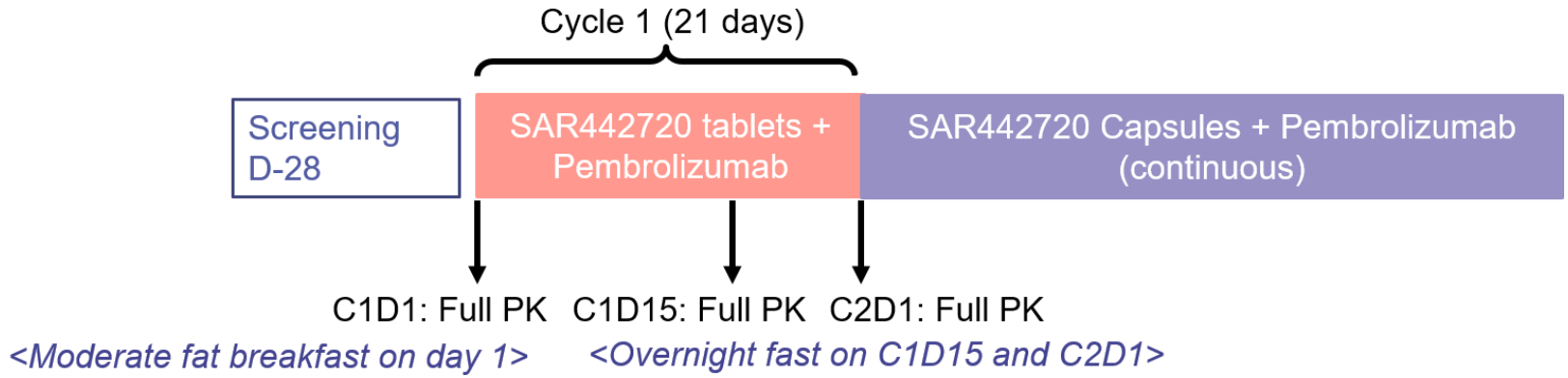
Abbreviations: D = day, DL = dose level, IV = intravenous, NSCLS = non-small cell lung cancer, PD1 = programmed cell death protein 1, PD-L1 = programmed death-ligand 1; Pembro = pembrolizumab, RP2D = recommended Phase 2 dose, TPS = Tumor Proportion Score.

Figure 3 - Graphical study design of SAR442720 and adagrasib for Part-3



Abbreviations: D = day, BID = twice daily, BIW = twice a week, DL = dose level, DLT = dose-limiting toxicity, NSCLS = non-small cell lung cancer, RP2D = recommended Phase 2 dose.

Figure 4 - Graphical study design of SAR442720 and pembrolizumab for Part-4



Abbreviations: C= cycle, D = day, PK = pharmacokinetics.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 2 - Schedule of activities (SOA) for Part-1 and Part-4

Procedure (Part-1 and Part-4)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes E/D=Early Discontinuation
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
Clinical Assessments										
Informed consent	X									Obtain written informed consent from the participant before any protocol required procedures and assessments are performed. Standard of care evaluations performed as part of the participant's routine treatment prior to signing consent may be used if they were done in the timeframe required for screening.
Inclusion and exclusion criteria	X									Recheck clinical status before 1st dose of study intervention.
Demography	X									Demographic information includes: age, gender, race, and ethnicity.
Full physical examination		X	X	X	X	X		X		Complete physical examination should be performed during screening, D1, D8, D15 of C1 and D1 of each cycle starting at C2, and at EOT. See Section 8.2.1 for details
Medical history	X									Prior cancer history includes: (i) date of diagnosis, (ii) staging, (iii) all previous therapies (ie, chemotherapy, immunotherapy, biologic or targeted agents, experimental therapies, radiotherapy, and surgery), (iv) previous therapy details (ie, regimen, start and stop dates), (v) best response for each regimen, and (vi) date of relapse or disease progression.

Procedure (Part-1 and Part-4)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes E/D=Early Discontinuation
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
Past and current medical conditions	X									
Documentation of tumor genotypic mutations	X									Documentation of at least one of the following genotypic mutations is required: KRAS amplification or mutations of KRASG12, NF1 LOF, or BRAF Class 3 mutations. See inclusion criteria for specific genotype/histotype requirement.
ECOG performance status		X	X			X		X		ECOG performance status to be assessed at screening, C1D1, and D1 of each subsequent cycle beginning at C2, and at EOT.
Vital signs		X	X	X	X	X	X	X		Vital signs should be taken prior to administration of study intervention. See Section 8.2.2 for details.
Body weight and height			X		X	X		X		Baseline height is required. Weight should be measured at baseline (predose C1D1), C1D15, D1 of each subsequent cycle, and at EOT.
Ophthalmic examination including retinal examination with OCT	X					X		X		Ophthalmic examination should be performed by an ophthalmologist during screening, between C2D1 to D7, then every 3 cycles, and EOT. See Section 8.2.7 for details.
Head MRI	X									Required within 4 weeks of C1D1 for participants with previous history of brain metastases. See Section 5.2, E 03.
Pregnancy test (WOCBP only)		X	X			X		X		For females of childbearing potential (including tubal ligation), perform a blood pregnancy test at screening and a urine/blood pregnancy test predose on D1 of each cycle, as well as at the EOT. See Section 10.2 for details.

Procedure (Part-1 and Part-4)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes E/D=Early Discontinuation
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
Coagulation tests		X	X			C3D1 then QO cycle		X		C1D1 hematology, chemistry, and coagulation samples are not required, if they were obtained within the previous 72 hours as part of screening. Participants receiving anticoagulation in which PT/aPTT (or partial thromboplastin time [PTT]) may be affected, should undergo additional monitoring on D1 at least every other cycle starting with C3D1 and then at EOT. Additional testing may be performed as clinically indicated. See Section 10.2 for details.
Laboratory assessments (including liver chemistries)		X	X	X	X	X	X	X		C1D1 hematology, chemistry, and coagulation samples are not required, if they were obtained within the previous 72 hours as part of screening. Testing must be performed and reviewed before dosing on C1D1. See Section 10.2 for details. C2+Day 15 laboratory assessments could be done remotely if needed and after discussion with the Study Medical Manager.
12-lead ECG		X	X		X	C3D1 then QO cycle		X		A single pre dose ECG should be obtained on C1D1 and C1D15 and then D1 of every 2 cycles starting at C3 (eg, C3D1, C5D1, etc) and at EOT See Section 8.2.4.
Hepatitis B and C	X									See Section 10.2.
Urinalysis		X	X			X				See Section 10.2.

Procedure (Part-1 and Part-4)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes E/D=Early Discontinuation
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
ECHO/MUGA	X					C2 D1-D7 then Q3 cycle		X		ECHO is the preferred methodology to measure LVEF. MUGA scan may be used if ECHO is not available or not technically feasible. However, the same methodology should be used throughout the study. Assessments should be performed during screening, C2 D1-7, every 3 cycles thereafter, and EOT, and as clinically indicated. If a participant does not complete 2 cycles of study intervention, the EOT assessment of LVEF is not required unless clinical signs or symptoms warrant an examination. Images will be collected and stored for possible central review.
CPK (total and MB isoenzyme)			X			X		X		CPK levels should be obtained at C1D1, D1 of each cycle, EOT and as clinically indicated.
Telephone contact for survival follow-up[c]									X	
Tumor assessments										
CT/MRI scan	X					C3 D1, C5 D1, C7D1, then every 3 cycles		X		See Section 8.1.
RECIST tumor response assessment	X					C3 D1, C5 D1, C7D1, then every 3 cycles				See Section 8.1.

Procedure (Part-1 and Part-4)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes E/D=Early Discontinuation
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
PDy and biomarker assessments (only for Part-1)										
Archival tumor tissue (baseline tumor tissue is required, on-treatment and EOT biopsy is optional')	X									In case fresh tumor biopsy cannot be collected as required, archival tumor tissue should be available to be submitted between screening and end of treatment: a) 1 H&E slide and 10 x 10-micron slides (minimum 30% viable tumor volume), or b) 1 H&E slide and 20 × 4-micron slides (with minimum 30% viable tumor volume). FFPE blocks, with sufficient tissue to allow the required slides to be sectioned, can be provided.
Fresh tumor biopsy			X				X	X		Fresh tumor biopsies (applicable to Part-1 only) pre-treatment and C2D15 will be mandatory for participants enrolled in the study, unless the investigator determines that the tumor site is not amenable to biopsy and poses a significant risk to participant safety. The Sponsor will evaluate this requirement on a case-by-case basis, and archival tumor tissue should not be used to replace fresh tumor biopsy in more than 6 participants. Pre-treatment biopsy may be a biopsy which was completed within 6 months prior to C1D1 without any anti-cancer treatment administered in such timeframe. The on-treatment biopsy may be obtained at C2D15 with a window of ±7 days. Pre-treatment and on-treatment biopsy (C2D15 with a window of ±7 days) should be collected from the same lesion. An EOT biopsy will be requested but is not mandatory. See Section 8.6.

Procedure (Part-1 and Part-4)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes E/D=Early Discontinuation
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
Blood for immune cell profiling, cytokines, RNA and ctDNA biomarker			See Table 9 below (Part-1 only)							
Study intervention										
SAR442720 dosing			Continuous dosing (twice weekly)							SAR442720 is administrated orally at home or at the hospital. See Section 6.1.
Pembrolizumab dosing			Continuous dosing Q3W (Part-1 and Part-4) or Q6W (Part-4 only)							Pembrolizumab is administrated in IV infusion at the hospital. See Section 6.1.
Assessment and documentation of study compliance			←==========→							Participants should be instructed to bring their pills and diary to every visit.
AE review		X	←==========→					X		C1D1 predose and See Section 8.3.
SAE review		X	←==========→					X		C1D1 predose and See Section 8.3.
Concomitant medication review		X	←==========→					X		Record all concomitant medications including any prescription medications, over-the-counter preparations, and transfusions received by participant from 7 days preceding C1D1 through EOT.
PK assessments										
Plasma samples			See Table 5 (Part-1) and Table 8 (Part-4) below							Blood samples (1.5 mL/sample) will be collected and processed into plasma for SAR442720 PK analysis at the time points listed in Table 5 (Part-1) and Table 8 (Part-4).

Procedure (Part-1 and Part-4)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes E/D=Early Discontinuation
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
Serum samples			See Table 5 (Part-1) and Table 8 (Part-4) below							Blood samples (1.5 mL/sample) will be collected and processed into serum for pembrolizumab PK analysis at the time points listed in Table 5 (Part-1) and Table 8 (Part-4).

Abbreviations: AE = adverse event, aPTT = activated partial thromboplastin time, C = cycle, CPK = creatine phosphokinase, CT = computed tomography, ctDNA = circulating tumor DNA, D or d = day, ECG = electrocardiogram, ECHO = echocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, FFPE = formalin-fixed paraffin-embedded, H&E = hematoxylin and eosin, IV = intravenous LTFU = long-term follow-up, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, MUGA = multigated acquisition, NF1 = neurofibromin 1; OCT = optical coherence tomography, PD = pharmacodynamics, PK = pharmacokinetic(s), PT = prothrombin time, PTT = partial thromboplastin time, Q3W = once every 3 weeks, Q6W = once every 6 weeks QO = every other, RECIST = Response Evaluation Criteria in Solid Tumours, SAE = serious adverse event, WOCBP = women of child bearing potential.

a Screening window is 14 days unless otherwise specified. Informed consent as well as participant demographics, medical history including documentation of tumor genotypic mutations, screening hepatitis tests, CT/MRI scan, ECHO/MUGA scan, and ophthalmic examination may be obtained 28 days before C1D1.

b Participants who discontinue study treatment should complete the safety follow-up or EOT visit within 30 days (±5 days) after the last dose, or prior to new treatment, whichever is earlier. Participants who wish to withdraw from study intervention treatment should be encouraged to complete the EOT. If a participant chooses to withdraw from the study completely, the reason for withdrawal should be documented.

c Post-study follow-up for disease status: Participants who discontinue study intervention treatment with radiological or clinical PD at the end of a treatment visit who have not yet started treatment with another anti-cancer therapy will proceed with 3 months follow-up visits until initiation of another anti-cancer therapy, disease progression, death, or study cutoff date (whichever comes first).

Table 3 - Schedule of activities for Part-2

Procedure (Part-2)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
Clinical Assessments										
Informed consent	X									Obtain written informed consent from the participant before any protocol required procedures and assessments are performed. Standard of care evaluations performed as part of the participant's routine treatment prior to signing consent may be used if they were done in the timeframe required for screening.
Inclusion and exclusion criteria	X									Recheck clinical status before 1st dose of study intervention.
Demography	X									Demographic information includes: age, gender, race, and ethnicity.
Full physical examination		X	X			X		X		Complete physical examination should be performed during screening, D1 of Cycle 1 and D1 of each cycle starting at C2, and at EOT. See Section 8.2.1 for details
Medical history	X									Prior cancer history includes: (i) date of diagnosis, (ii) staging, (iii) all previous therapies (ie, chemotherapy, immunotherapy, biologic or targeted agents, experimental therapies, radiotherapy, and surgery), (iv) previous therapy details (ie, regimen, start and stop dates), (v) best response for each regimen, and (vi) date of relapse or disease progression.

Procedure (Part-2)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes
Day	-1 to -28	-1 to -14	1	8 (±1 d)	15 (±1 d)	1 (±2 d)	15 (±2 d)			
Past and current medical conditions	X									
Documentation of tumor genotypic mutations	X									Documentation of lack of known SHP2 inhibition resistant mutations is required. See exclusion criteria E 29.
ECOG performance status		X	X			X		X		ECOG performance status to be assessed at screening, C1D1, and D1 of each subsequent cycle beginning at C2, and at EOT.
Vital signs		X	X	X	X	X	X	X		Vital signs should be taken prior to administration of study intervention. See Section 8.2.2 for details.
Body weight and height			X			X		X		Baseline height is required. Weight should be measured at baseline (predose C1D1), C1D1, C1D15, D1 of each subsequent cycle, and at EOT.
Ophthalmic examination including retinal examination with OCT	X					X		X		Ophthalmic examination should be performed by an ophthalmologist during screening, between C2D1 to D7, then every 3 cycles and EOT. See Section 8.2.7 for details. Unscheduled ophthalmology consultation recommended per Investigator's discretion as clinically indicated
Head MRI	X									Required within 4 weeks of C1D1 for participants with previous history of brain metastases. See Section 5.2, E 03.

Procedure (Part-2)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes
Day	-1 to -28	-1 to -14	1	8 (±1 d)	15 (±1 d)	1 (±2 d)	15 (±2 d)			
Pregnancy test (WOCBP only)		X	X			X		X		For females of childbearing potential (including tubal ligation), perform a blood pregnancy test at screening and a urine/blood pregnancy test predose on D1 of each cycle, as well as at the EOT. See Section 10.2 for details.
Coagulation tests		X	X			C3D1 then QO cycle		X		C1D1 hematology, chemistry, and coagulation samples are not required, if they were obtained within the previous 72 hours as part of screening. Participants receiving anticoagulation in which PT/aPTT (or partial thromboplastin time [PTT]) may be affected, should undergo additional monitoring on D1 at least every other cycle starting with C3D1 and then at EOT. Additional testing may be performed as clinically indicated. See Section 10.2 for details.
Laboratory assessments (including liver chemistries)		X	X	X	X	X	X	X		C1D1 hematology, chemistry, and coagulation samples are not required, if they were obtained within the previous 72 hours as part of screening. Testing must be performed and reviewed before dosing on C1D1. See Section 10.2 for details. C2+Day 15 laboratory assessments could be done remotely if needed and after discussion with the Study Medical Manager.
12-lead ECG		X	X		X	C3D1 then QO cycle		X		A single pre dose ECG should be obtained on C1D1 and C1D15 and then D1 of every 2 cycles starting at C3 (eg, C3D1, C5D1, etc) and at EOT See Section 8.2.4.

Procedure (Part-2)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
Hepatitis B and C	X									See Section 10.2.
Urinalysis		X	X			X				See Section 10.2.
ECHO/MUGA	X					C2 D1-D7 then Q3 cycle		X		ECHO is the preferred methodology to measure LVEF. MUGA scan may be used if ECHO is not available or not technically feasible. However, the same methodology should be used throughout the study. Assessments should be performed during screening, C2 D1-7, every 3 cycles thereafter, and EOT, and as clinically indicated. If a participant does not complete 2 cycles of study intervention, the EOT assessment of LVEF is not required unless clinical signs or symptoms warrant an examination. Images will be collected and stored for possible central review.
CPK (total and MB isoenzyme)			X			X		X		CPK levels should be obtained at C1D1, D1 of each cycle, EOT and as clinically indicated.
Telephone contact for survival follow-up[c]									X	
Tumor assessments										
CT/MRI scan	X					Every 9 weeks (+/- 7 days)		X		RECIST tumor response assessment will be performed at the time of each scan. See Section 8.1.

Procedure (Part-2)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
PDy and biomarker assessments										
Archival tumor tissue	X									In case fresh tumor biopsy cannot be collected as required, archival tumor tissue should be obtained from biopsies done within 6 months to be submitted between screening and C2D15: a) 1 H&E slide 1 H&E slide and minimum 10 × 4-micron slides (with minimum 30% viable tumor volume). FFPE blocks, with sufficient tissue to allow the required slides to be sectioned, can be provided.
Fresh tumor biopsy			X				X	X		Fresh tumor biopsies are required per inclusion criteria. The on-treatment biopsy may be obtained at C2D15 with a window of ±7 days. On treatment and EOT biopsy are optional and should be collected from the same lesion as baseline. See Section 8.6.
Blood for immune cell profiling, cytokines, RNA and ctDNA biomarker			See Table 9 below							
Study intervention										
SAR442720 dosing			Continuous dosing (twice weekly)							SAR442720 is administrated orally at home or at the hospital. See Section 6.1.
Pembrolizumab dosing			Continuous dosing 200mg Q3W (or 400 mg Q6W)							Pembrolizumab is administrated in IV infusion at the hospital. See Section 6.1.

Procedure (Part-2)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	LTFU (every 3 months ±2 wks)[c]	Notes
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**			
Assessment and documentation of study compliance			←==========→							Participants should be instructed to bring their pills and diary to every visit.
AE review		X	←==========→					X		Predose on C1D1 also see Section 8.3.
SAE review		X	←==========→					X		Predose on C1D1 also see Section 8.3.
Concomitant medication review		X	←==========→					X		Record all concomitant medications including any prescription medications, over-the-counter preparations, and transfusions received by participant from 7 days preceding C1D1 through EOT.
PK assessments										
Plasma samples			See Table 5 below							Blood samples (1.5 mL/sample) will be collected and processed into plasma for SAR442720 PK analysis at the time points listed in Table 5.
Serum samples			See Table 5 below							Blood samples (1.5 mL/sample) will be collected and processed into serum for pembrolizumab PK analysis at the time points listed in Table 5.

Abbreviations: AE = adverse event, aPTT = activated partial thromboplastin time, C = cycle, CPK = creatine phosphokinase, CT = computed tomography, ctDNA = circulating tumor DNA, D or d = day, ECG = electrocardiogram, ECHO = echocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, FFPE = formalin-fixed paraffin-embedded, H&E = hematoxylin and eosin, IV = intravenous, LTFU = long-term follow-up, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, MUGA = multigated acquisition, OCT = optical coherence tomography, PD = pharmacodynamics, PK = pharmacokinetic(s), PT = prothrombin time, PTT = partial thromboplastin time, Q3W = once every 3weeks, Q3W = once every 3weeks, QO = every other, RECIST = Response Evaluation Criteria in Solid Tumours, SAE = serious adverse event, SHP2 = Src Homology region 2 domain-containing protein tyrosine phosphatase 2. WOCBP = women of child bearing potential.

a Screening window is 14 days unless otherwise specified. Informed consent should be signed before any study specific procedures; it can be signed more than 28 days prior to initiating study treatment. Participant demographics, medical history including documentation of tumor genotypic mutations, screening hepatitis tests, CT/MRI scan, ECHO/MUGA scan, and ophthalmic examination may be obtained 28 days before C1D1.

b Participants who discontinue study treatment should complete the safety follow-up or EOT visit within 30 days (±5 days) after the last dose, or prior to new treatment, whichever is earlier. Participants who wish to withdraw from study intervention treatment should be encouraged to complete the EOT. If a participant chooses to withdraw from the study completely, the reason for withdrawal should be documented.

c Post-study follow-up for disease status: Participants who discontinue study treatment with radiological or clinical PD at the end of a treatment visit who have not yet started treatment with another anti-cancer therapy will proceed with 3 months follow-up visits until initiation of another anti-cancer therapy, disease progression, death, or study cutoff date (whichever comes first).

Table 4 - Schedule of activities for Part-3

Procedure (Part-3)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	Notes
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**		
Clinical Assessments									
Informed consent	X								Obtain written informed consent from the participant before any protocol required procedures and assessments are performed. Standard of care evaluations performed as part of the participant's routine treatment prior to signing consent may be used if they were done in the timeframe required for screening.
Inclusion and exclusion criteria	X								Recheck clinical status before 1st dose of study intervention.
Demography	X								Demographic information includes: age, gender, race, and ethnicity.
Full physical examination		X	X			X		X	Complete physical examination should be performed during screening, D1 of Cycle 1 and D1 of each cycle starting at C2, and at EOT.
Medical history	X								Prior cancer history includes: (i) date of diagnosis, (ii) staging, (iii) all previous therapies (ie, chemotherapy, immunotherapy, biologic or targeted agents, experimental therapies, radiotherapy, and surgery), (iv) previous therapy details (ie, regimen, start and stop dates), (v) best response for each regimen, and (vi) date of relapse or disease progression.
Past and current medical conditions	X								
Documentation of tumor genotypic mutations	X								
ECOG performance status		X	X			X		X	ECOG performance status to be assessed at screening, C1D1, and D1 of each subsequent cycle beginning at C2, and at EOT.

Procedure (Part-3)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	Notes
Day	-1 to -28	-1 to -14	1	8 (±1 d)	15 (±1 d)	1 (±2 d)	15 (±2 d)		
Vital signs		X	X	X	X	X	X	X	Vital signs should be taken prior to administration of study intervention. See protocol for details.
Body weight and height			X		X	X		X	Baseline height is required. Weight should be measured at baseline (predose C1D1), C1D15, D1 of each subsequent cycle, and at EOT.
Ophthalmic examination including retinal examination with OCT	X					X		X	Ophthalmic examination should be performed by an ophthalmologist during screening, and EOT. Unscheduled ophthalmology consultation recommended per Investigator's discretion as clinically indicated
Head MRI	X								Required within 4 weeks of C1D1 for participants with previous history of brain metastases.
Pregnancy test (WOCBP only)		X	X			X		X	For females of childbearing potential (including tubal ligation), perform a blood pregnancy test at screening and a urine/blood pregnancy test predose on D1 of each cycle, as well as at the EOT.
Coagulation tests		X	X			C3D1 then QO cycle		X	Additional testing may be performed as clinically indicated.
Laboratory assessments (including liver chemistries)		X	X	X	X	X	X	X	C1D1 hematology, chemistry, and coagulation samples are not required, if they were obtained within the previous 72 hours as part of screening. Testing must be performed and reviewed before dosing on C1D1. C2+Day 15 laboratory assessments could be done remotely if needed and after discussion with the Study Medical Manager.
12-lead ECG		X	X		X	C3D1 then QO cycle		X	A single pre dose ECG should be obtained on C1D1 and C1D15 and then D1 of every 2 cycles starting at C3 (eg, C3D1, C5D1, etc) and at EOT. Unscheduled ECGs to be obtained in case of signs and symptoms, and as per Investigator's assessment.

Procedure (Part-3)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	Notes
Day	**-1 to -28**	**-1 to -14**	**1**	**8 (±1 d)**	**15 (±1 d)**	**1 (±2 d)**	**15 (±2 d)**		
Hepatitis B and C	X								
Urinalysis		X	X			X			
ECHO/MUGA	X					C2 D1-7 then Q3 cycle		X	ECHO is the preferred methodology to measure LVEF. MUGA scan may be used if ECHO is not available or not technically feasible. However, the same methodology should be used throughout the study. Assessments should be performed during screening, C2 D1-7, every 3 cycles thereafter, and EOT, and as clinically indicated.
CPK (total and MB isoenzyme)			X			X		X	CPK levels should be obtained at C1D1, D1 of each cycle, EOT and as clinically indicated.
Tumor assessments									
CT/MRI scan	X					Every 6 weeks (+/- 7 days)		X	RECIST tumor response assessment will be performed at the time of each scan.
PDy and biomarker assessments									
Archival tumor tissue	X								In case fresh tumor biopsy cannot be collected as required, archival tumor tissue should be obtained from biopsies done within 6 months to be submitted between screening and C2D15.
Fresh tumor biopsy			X		X			X	Fresh tumor biopsy is optional in dose escalation (Part-3A). Fresh tumor biopsy is required in dose expansion (Part-3B). The on-treatment and EOT biopsies are optional, on-treatment biopsy may be obtained at C1D15 with a window of +7 days. On treatment and EOT biopsy should be collected from the same lesion as baseline.
ctDNA biomarker			See Table 10 below						
Study intervention									
SAR442720 dosing			Continuous dosing (twice weekly)						SAR442720 is administrated orally at home or at the hospital.

Procedure (Part-3)	Screening[a]		Cycle 1 (21-day cycle)			Cycles 2+ (21-day cycle)		EOT (within 30 ±5d of last dose)[b]	Notes
Day	-1 to -28	-1 to -14	1	8 (±1 d)	15 (±1 d)	1 (±2 d)	15 (±2 d)		
Adagrasib			Continuous dosing (twice daily)						Adagrasib is administrated orally at home or at the hospital.
Assessment and documentation of study compliance			←==========→						Participants should be instructed to bring their pills and diary to every visit.
AE review		X	←==========→					X	Predose on C1D1 also See Section 8.3
SAE review		X	←==========→					X	Predose on C1D1 also See Section 8.3
Concomitant medication review		X	←==========→					X	Record all concomitant medications including any prescription medications, over the counter preparations, and transfusions received by participant from 7 days preceding C1D1 through EOT.
SAR442720 PK samples			See Table 6 below						Blood samples (1.5 mL/sample) will be collected and processed into plasma for SAR442720 PK analysis at the time points listed in Table 6 and Table 7.
Adagrasib PK samples			See Table 7 below						Blood samples (1.5 mL/sample) will be collected and processed into plasma for adagrasib PK analysis at the time points listed in Table 6 and Table 7.

Abbreviations: AE = adverse event, C = cycle, CPK = creatine phosphokinase, CT = computed tomography, ctDNA = circulating tumor DNA, D or d = day, ECG = electrocardiogram, ECHO = echocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, IV = intravenous, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, MUGA = multigated acquisition, OCT = optical coherence tomography, PK = pharmacokinetic(s), QO = every other, RECIST = Response Evaluation Criteria in Solid Tumours, SAE = serious adverse event, WOCBP = women of child bearing potential.

a Screening window is 14 days unless otherwise specified. Informed consent should be signed before any study specific procedures, it can be signed more than 28 days prior to initiating study treatment. Participant demographics, medical history including documentation of tumor genotypic mutations, screening hepatitis tests, CT/MRI scan, ECHO/MUGA scan, and ophthalmic examination may be obtained 28 days before C1D1.

b Participants who discontinue study treatment should complete the safety follow-up or EOT visit within 30 days (±5 days) after the last dose, or prior to new treatment, whichever is earlier. Participants who wish to withdraw from study intervention treatment should be encouraged to complete the EOT. If a participant chooses to withdraw from the study completely, the reason for withdrawal should be documented.

Table 5 - PK time points for Part-1 and Part-2

SAR442720			Pembrolizumab		
Study Day	**PK Time points[a]**	**Window[b]**	**Study Day**	**PK Time points[a]**	**Window[b]**
Cycle 1					
Day 1	Predose[c]	Within 1 hour before Day 1 dose	Day 1	Predose[c]	Within 1 hour before Day 1 dose
	2 hours	±10 minutes		Postdose	<30 min after end of infusion
	8 hours[e]	±30 minutes			
Day 8[d]	Predose	Within 1 hour before Day 8 dose			
Day 15	Predose	Within 1 hour before Day 15 dose			
Cycle 2					
Day 1	Predose[c]	Within 1 hour before Day 1 dose	Day 1	Predose[c]	Within 1 hour before Day 1 dose
	2 hours	±10 minutes			
	8 hours[e]	±30 minutes			
Day 2[d]	2 hours[e]	±10 minutes			
Cycle 6					
Day 1	Predose[c]	Within 1 hour before Day 1 dose	Day 1	Predose[c]	Within 1 hour before Day 1 dose
EOT	X	Any time during visit			

Abbreviations: EOT = end of treatment; PK = pharmacokinetic(s).

a PK samples = one 1.5 mL sample required per time point.

b Windows are relative to the nominal time point.

c PK samples for SAR442720 and pembrolizumab will be collected at the same time points.

d Only for Day 1, Day 2 of each weekly dosing schedule

e Only collected during Part-1.

Table 6 - PK time points (Part-3A dose escalation)

	SAR442720		Adagrasib	
Study Day	**PK Time points[a]**	**Window[b]**	**PK Time points[a]**	**Window[b]**
Cycle 1				
Day 1	Predose 0.5 hour[c] 1 hour 2 hours 4 hours 6 hours	Within 1 hour before Day 1 dose ±10 minutes ±10 minutes ±10 minutes ±10 minutes ±30 minutes	Predose 1 hour 2 hours 4 hours 6 hours 8 hours[d] 12 hours[d]	Within 1 hour before Day 1 morning dose ±10 minutes ±10 minutes ±10 minutes ±30 minutes ±30 minutes Within 1 hour before D1 evening dose
Day 2	24 hours after D1 dose	Within 1 hour before Day 2 dose	12 hours after D1 evening dose	Within 1 hour before D2 morning dose
Day 8	Predose	Within 1 hour before Day 8 dose	Predose	Within 1 hour before Day 8 morning dose
Day 15	Predose 0.5 hour[c] 1 hour 2 hours 4 hours 6 hours	Within 1 hour before Day 15 dose ±10 minutes ±10 minutes ±10 minutes ±10 minutes ±30 minutes	Predose 1 hour 2 hours 4 hours 6 hours 8 hours[d]	Within 1 hour before Day 15 morning dose ±10 minutes ±10 minutes ±10 minutes ±30 minutes ±30 minutes
Day 16	24 hours after D15 dose 2 hours[c]	Within 1 hour before Day 16 dose ±10 minutes	12 hours after D15 evening dose -	Within 1 hour before Day 16 morning dose -
Cycle 2, 3 and Cycle 4				
Day 1	Predose	Within 1 hour before Day 1 dose	Predose	Within 1 hour before Day 1 dose
EOT	X	Any time during visit	X	Any time during visit

Abbreviations: EOT = end of treatment, PK = pharmacokinetic(s).

a For samples where both SAR442720 and adagrasib are collected, they could be collected at the same time points.

b Windows are relative to the nominal time point.

c SAR442720 only PK samples.

d Adagrasib only PK sample, 12-hour sample on Day 1 is optional to collect.

Table 7 - PK time points (Part-3B Dose Expansion)

	SAR442720		Adagrasib	
Study Day	**PK Time points[a]**	**Window[b]**	**PK Time points[a]**	**Window[b]**
Cycle 1				
Day 1	Predose	Within 1 hour before Day 1 dose	Predose	Within 1 hour before Day 1 morning dose
	2 hours[c]	±10 minutes	-	-
	6 hours	±30 minutes	6 hours	±30 minutes
Day 8	Predose	Within 1 hour before Day 8 dose	Predose	Within 1 hour before Day 8 morning dose
Day 15	Predose	Within 1 hour before Day 15 dose	Predose	Within 1 hour before Day 15 morning dose
	2 hours[c]	±10 minutes	-	-
	6 hours	±30 minutes	6 hours	±30 minutes
Cycle 2, 3 and 4				
Day 1	Predose	Within 1 hour before Day 1 dose	Predose	Within 1 hour before Day 1 dose
EOT	X	Any time during visit	X	Any time during visit

Abbreviations: EOT = end of treatment, PK = pharmacokinetic(s).

a For samples collected for both SAR442720 and adagrasib can be collected at the same time points.

b Windows are relative to the nominal time point.

c SAR442720 only PK samples.

Table 8 - PK time points for Part-4

SAR442720			Pembrolizumab		
Study Day	**PK Time points[a]**	**Window[b]**	**Study Day**	**PK Time points[a]**	**Window[b]**
Cycle 1					
Day 1	Predose[c] 0.5 hour 1 hour 2 hours 4 hours 8 hours	Within 1 hour before Day 1 dose ±5 minutes ±10 minutes ±10 minutes ±30 minutes ±30 minutes	Day 1	Predose[c] Postdose	Within 1 hour before Day 1 dose <30 min after end of infusion
Day 2	24 hours post Day 1 dose	Within 1 hour before Day 2 dose	-	-	-
Day 8	Predose	Within 1 hour before Day 8 dose	-	-	-
Day 15	Predose[c] 0.5 hour 1 hour 2 hours 4 hours 8 hours	Within 1 hour before Day 1 dose ±5 minutes ±10 minutes ±10 minutes ±30 minutes ±30 minutes	-	-	-
Day 16	24 hours post Day 15 dose	Within 1 hour before Day 16 dose	-	-	-
Cycle 2					
Day 1	Predose[c] 0.5 hour 1 hour 2 hours 4 hours 8 hours	Within 1 hour before Day 1 dose ±5 minutes ±10 minutes ±10 minutes ±30 minutes ±30 minutes	Day 1	Predose[c]	Within 1 hour before Day 1 dose
Day 2	24 hours post Day 1 dose	Within 1 hour before Day 2 dose	-	-	-
Cycle 6					
Day 1	Predose[c]	Within 1 hour before Day 1 dose	Day 1	Predose[c]	Within 1 hour before Day 1 dose
EOT	X	Any time during visit	-	-	-

Abbreviations: EOT = end of treatment,; PK = pharmacokinetic(s).

a PK samples = one 1.5 mL sample is required per time point.

b Windows are relative to the nominal time point.

c PK samples for SAR442720 and pembrolizumab will be collected at the same time points.

Table 9 - Pharmacodynamic/biomarker sampling time points (Part-1 and Part-2)

Study Day	RNABiomarker Time points[a]	Blood germline testings[b]	ctDNA Biomarker Time points[c]	Immune cell profiling time points[d]	Cytokines time points[e]	Window[f]
Cycle 1						
Day 1	Predose	Predose	Predose	Predose	Predose	Within 1 hour before Day 1 dose
Day 15	Trough		Trough	Trough	Trough	
	-		-	-	-	Within 1 hour before Day 15 dose
	-		-	-	-	
	-		-	-	-	
	-		-	-	-	
Cycles 2, 3, and 4						
Day 1	Predose		Predose	Predose	Predose	Within 1 hour before dose
EOT	X		X	X	X	Any time during visit

Abbreviations: C = cycle, ctDNA = circulating tumor DNA, D = day, EOT = end of treatment

a RNA biomarkers: 3 mL sample is required per time point.

b Blood sample collected at baseline will be used as the germline control from consenting participants.

c ctDNA biomarkers: 10 mL sample required per time point. Baseline or C1D1 predose of ctDNA biomarker will be collected from all participants. On-treatment of ctDNA biomarker (From C1D15 to EOT) will only be collected from participants in the dose-expansion cohorts.

d Immune cell profiling biomarkers: 8 mL sample is required per time point.

e Cytokine biomarkers: 4mL sample is required per time point.

f Windows are relative to the nominal time point.

Table 10 - Pharmacodynamic/Biomarker sampling time points for Part-3

Study Day	ctDNA Biomarker Time points[a]	Window[b]
Cycle 1		
Day 1	Predose	Within 1 hour before Day 1 dose
Day 15	Trough	Within 1 hour before Day 15 dose
Cycles 2, 3, and 4		
Day 1	Predose	Within 1 hour before dose
EOT	X	Any time during visit

Abbreviations: C = cycle, ctDNA = circulating tumor DNA, D = day; EOT = end of treatment.

a ctDNA biomarkers: 10 mL sample required per time point. Baseline or C1D1 predose of ctDNA biomarker will be collected from all participants. On-treatment of ctDNA biomarker (From C1D15 to EOT) will only be collected from participants in the dose-expansion cohorts.

b Windows are relative to the nominal time point.

2 INTRODUCTION

SAR442720 (also known as RMC-4630) is a potent, selective, and orally bioavailable SHP2 allosteric inhibitor that is being developed for participants with tumors harboring certain activating mutations or other genotypic aberrations in the RAS–mitogen-activated protein kinase (MAPK) pathway, including upstream mutations in receptor tyrosine kinases (RTKs).

2.1 STUDY RATIONALE

The RAS-MAPK pathway is frequently dysregulated in human cancers, typically as a result of genomic alterations that lead to hyperactivation (5). These alterations can occur at 3 levels: upstream of RAS in RTKs, directly within mediators of the RAS catalytic cycle (RAS isoforms and RAS GTPase activating proteins [GAPs], such as neurofibromin 1 [NF1]), or in downstream effector kinases, such as BRAF or MEK (6).

SAR442720 is a potent, selective, and orally bioavailable SHP2 allosteric inhibitor. SHP2 is a positive upstream regulator of RAS activation, and thus, presents a suitable therapeutic target for patients whose tumors harbor oncogenic mutations that remain dependent on active RAS cycling between GTP- and GDP-bound state. Examples of these include subsets of KRASG12, NF1 LOF mutations, class 3 type mutations in BRAF (7, 8) or amplification of wild-type KRAS (9).

SHP2 is also involved in signaling in T-cells. It binds with PD-1 following PD-L1 stimulation and inhibits T-cell activation. Therefore, targeting SHP2 may restore or even enhance T-cell functions. The costimulatory receptor CD-28, and to some extent the T-cell receptor, are dephosphorylated and de-activate some critical components of the interferon gamma (IFNγ) signaling cascade, defects in which have been described as a key component of resistance to anti-PD1 therapy. SHP2 inhibition may increase the efficacy of PD1 inhibitors in patients with high PD-L1 expression but may also sensitize patients with low PD-L1 expression to a PD1 inhibitor (1, 2).

SHP2 is expressed in immune cells and plays a role in signal transduction downstream of regulatory immunoreceptors, including PD-1 (10). Preclinical studies have demonstrated a role for SHP2 in tumor immunity through modulation of both innate and adaptive mechanisms. In particular, allosteric inhibition of SHP2 has been shown to increase CD8+T cell tumor infiltrates and to deplete pro-tumorigenic tumor associated macrophages through attenuation of CSF-1 receptor signaling (11). Consistent with a pleiotropic effect on the immune system, SHP2 inhibition has been shown to attenuate tumor growth in syngeneic models of mouse tumors that are apparently insensitive to a direct, cell intrinsic effect of SHP2 inhibition (12, 13, 14). Given the potential complementary mechanisms of action, SAR442720 plus anti-PD-1 represents a rational combination which was evaluated in preclinical models.

[redacted]

[redacted]

Preclinical testing confirms that SHP2 inhibition does not confer sensitivity to PD1 refractory tumors (11). In addition, the preliminary observations from patients receiving single agent SAR442720 suggest increased T-cell infiltration and activation of innate immune system in tumors during SHP2i treatment. Considering that SHP2 plays vital roles in tumor growth and tumor immunity, so combination of SAR442720 with anti-PD1 therapy would provide a promising therapeutic strategy.

The purpose of the escalation part (Part-1) is to evaluate the safety, PK, and preliminary efficacy of escalating doses of SAR442720 in combination with pembrolizumab in adult participants with relapsed/refractory solid tumors with specific mutations/rearrangements that result in hyperactivation of the RAS-MAPK pathway and to identify the RP2D for this combination.

The purpose of the expansion part (Part-2) is to evaluate the anti-tumor activity and safety of SAR442720 combined with pembrolizumab in first-line treatment of participants with advanced NSCLC.

The purpose of Part-3 (Part-3A: dose escalation and Part-3B: dose expansion) of this study is to evaluate the safety, recommended Phase 2 dose (RP2D), anti-tumor effect, and PK of SAR442720 in combination with KRAS G12C inhibitor, adagrasib in participants with NSCLC harboring KRAS G12C mutations.

The purpose of Part-4 of this study is to evaluate the effect of food on the PK of SAR442720 tablet and the relative bioavailability of SAR442720 tablet formulation (test) compared to the SAR442720 capsule formulation (reference), when dosed in combination with pembrolizumab to participants with advanced malignancies.

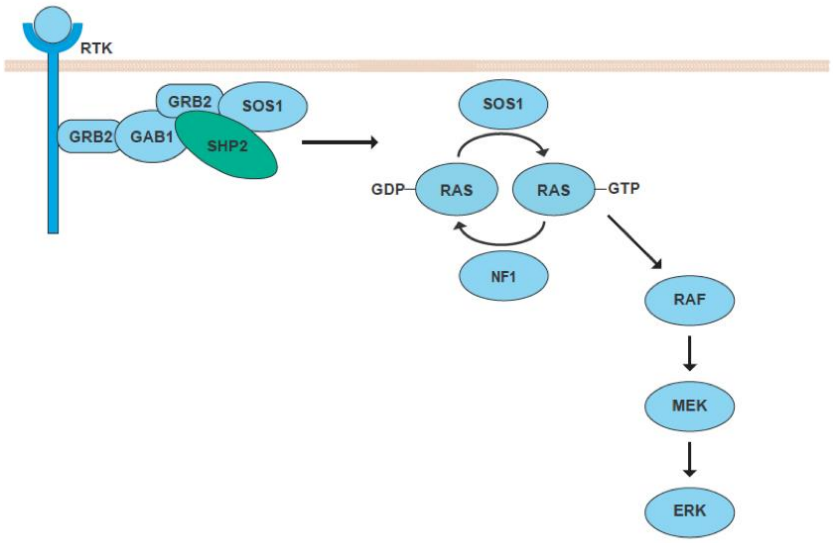
2.2 BACKGROUND

SHP2 is a non-receptor protein tyrosine phosphatase and scaffold protein that functions downstream of multiple RTKs, integrating cell surface growth factor signals to promote RAS activation (Figure 5). SAR442720 was designed as a potent and selective SHP2 allosteric inhibitor that suppresses RAS activation and the proliferation in cancers that, distinct from those dependent on oncogenic RTKs, are driven by nucleotide cycling oncogenic point mutations (eg, KRAS G12C) and wild-type amplification of KRAS and other RAS-GTP dependent downstream mutations, eg, NF1 LOF, or RAS-GTP dependent oncogenic BRAF Class 3 (9, 15).

2.2.1 Pembrolizumab mechanism of action

Pembrolizumab is a human PD-1-blocking monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Figure 5 - The RAS-MAPK pathway demonstrating the convergence nodal position of SHP2 in the pathway



2.2.2 Adagrasib mechanism of action

Adagrasib (MRTX849) is an orally available small molecule that elicits anti-tumor activity through selective, covalent binding to and inhibition of the KRAS G12C mutant variant. Adagrasib effectively inhibits KRAS signaling and demonstrates cytoreductive anti-tumor activity in KRAS G12C-mutant models. Adagrasib demonstrated potent inhibition of KRAS-dependent signal transduction and cancer cell viability, and selectivity of > 1000 × for KRAS G12C compared with KRAS wild-type. Adagrasib inhibited tumor cell growth and viability in cells harboring KRAS G12C mutations, but not in cells with wild-type KRAS or other KRAS mutations. Adagrasib demonstrated broad-spectrum anti-tumor activity across a panel of KRAS G12C-positive patient- or cell-derived tumor models implanted in mice at well-tolerated dose levels including complete tumor responses in a subset of models (16). Collectively, these results support the evaluation of adagrasib in patients with malignancies having KRAS G12C mutations.

2.2.3 Rationale for NSCLC

Worldwide, lung cancer remains the leading cause of cancer incidence and its mortality is projected to reach 2.45 million worldwide by 2030, a 39% increase in just over a decade (17). NSCLC accounts for approximately 85% of all lung cancer cases, with 2 broad histologic subtypes, squamous cell carcinoma and non-squamous cell carcinoma (majority is adenocarcinoma) (18).

2.2.4 Current standard of care in NSCLC

Prominent adaptive anti-tumor immune responses have been documented by direct analysis of immune cell populations and indirectly by measuring tumor PD-L1 expression, interferon gamma–related signatures, or multimarker transcriptomic profiles (19, 20, 21, 22). Using immunohistochemistry (IHC), PD-L1 expression in greater than or equal to 1% of tumor cells has been reported in approximately 60% of advanced NSCLC and with high levels (eg, ≥50% of tumor cells) in 25% to 30% of cases (23, 24).

The KEYNOTE 024 trial reported a significant improvement in overall survival (OS) for pembrolizumab monotherapy in an equally selected population, mostly generated in the subgroup of patients with high PD-L1 expression (≥50%) (25). In the KEYNOTE 042 trial, a significant benefit with 1L pembrolizumab compared with platinum-based chemotherapy was revealed by using a lower selection threshold, PD-L1 ≥1% (26). The KEYNOTE 021 trial was the first Phase 2 randomized study reporting improved outcome (ORR: 56.7% versus 30.2%; PFS: 24.0 months versus 9.3 months; and OS: not reached versus 21.1 months) with upfront pembrolizumab-chemotherapy combinations in unselected patients with non-squamous advanced NSCLC compared with chemotherapy alone (platinum plus pemetrexed) (27). These results were confirmed by the Phase 3 KEYNOTE 189 trial in all PD-L1 subsets, even PD-L1-negative tumors (28). Pembrolizumab is therefore approved in combination with platinum and pemetrexed as the first line therapy for non-squamous NSCLC in both the European Union (EU) (29) and the US (30). Pembrolizumab monotherapy is also approved as the first-line therapy to treat patients with TPS ≥1% NSCLC in the US, and to treat patients with NSCLC TPS ≥50% in the EU.

2.2.5 Rationale for combining SAR442720 with pembrolizumab

The anti-tumor activity observed in in-vitro studies and in vivo mouse studies of SAR442720 in the presence of an anti-PD1 antibody is described in Section 2.1.

Both preclinical studies and preliminary clinical biomarker data suggest SAR442720 could modulate tumor immune microenvironment, characterized by an increase in CD8+T cell infiltration and selective decrease of pro-tumorigenic macrophages in tumor tissue. The immune permissive tumor microenvironment modulation by SAR442720 could synergize with pembrolizumab to enhance anti-tumor activity (11).

Therefore, this expansion part, Cohort A1 and Cohort A2, will further assess the potential synergistic activity of SAR442720 with pembrolizumab in first-line treatment in different cohorts of participants with advanced NSCLC, from an anti-tumor activity and safety standpoint.

2.2.6 Rationale for combining SAR442720 with adagrasib

Nonclinical and clinical studies observations with RAF inhibitors have suggested that inhibition of RAS signaling may be transient due to feedback activation. Mechanistic studies have shown that such adaptive resistance may be mediated by SHP2 (31), and clinical trial observations have implicated RTK signaling (32, 33).

The combination of SAR442720 and adagrasib may augment anti-tumor activity through inhibition of feedback activation and consequently prevent resistance. Although inhibitors of KRAS G12C covalently bind to mutant cysteine in KRAS G12C in its GDP-bound state (34, 35), KRAS G12C continues to cycle between GTP and GDP states, and KRAS G12C retains the ability to transduce upstream activation into downstream signaling (36, 37). Thus, the addition SAR442720 to adagrasib may promote anti-tumor activity by inhibiting the cycling to GTP-bound KRAS for both mutant and wild type KRAS species, therefore theoretically preventing resistance.

In vivo experiments were conducted with MRTX849 and the SHP2 inhibitor RMC-4550 to evaluate the anti-tumor activity of the combination in five KRAS G12C-mutant human tumor xenograft models grown in immunocompromised mice. RMC-4550 was selected as a prototype SHP2 inhibitor for proof-of-concept nonclinical combination studies as it is the most active and best characterized of all SHP2 inhibitors reported to date (37). As RMC-4550 was reported to be highly selective for SHP2 and demonstrated clear target-mediated activity in nonclinical studies, it is proposed as a suitable surrogate prototype SHP2 target class inhibitor for proof-of-concept combination anti-tumor efficacy studies. The combination of MRTX849 and RMC-4550 elicited significant anti-tumor activity compared to single agent treatment in all five models. The effect of the combination compared to the single agent effect was pronounced in some models. For example, in the KYSE-410 model, treatment with either single agent resulted in stable disease whereas the combination elicited near complete response. In addition, the KYSE-410 and SW1573 models were two of the xenograft models least sensitive to MRTX849 single agent treatment in a previous survey of models (16), suggesting SHP2 inhibition may address mechanisms that limit the effectiveness of single agent MRTX849 treatment. The increased combination anti-tumor activity was observed in tumor models derived from multiple cancer types suggesting the combination of MRTX849 and a SHP2 inhibitor may be broadly active in multiple cancer types. In summary, the combination of MRTX849 and a SHP2 inhibitor exhibited increased anti-tumor activity in multiple in vivo models compared to single agent treatment and these data provide rationale for combining these agents for the treatment of cancer.

The KRAS G12C mutation occurs frequently in NSCLC (14%) and effective targeted therapies for cancers with KRAS mutations remain an unmet medical need. KRAS G12C mutant NSCLC patients showed a variable and submaximal response to KRAS G12C inhibitors; objective response rate (ORR) to sotorasib, another KRAS G12C inhibitor that was granted accelerated approval for NSCLC patients, was 37% (4) and ORR to adagrasib was 45% (3). In addition, it was shown in mouse model that treatment with MRTX849 remodeled the tumor immune microenvironment and was able to produce sustained complete response when combined with check point inhibitors in immune competent animals but not in T-cell deficient mice (38). These data suggest that SHP2 inhibition in combination with KRAS G12C inhibitor has potential to enhance the anti-tumor activity by blocking the receptor tyrosine kinase resistance mechanisms as well as by contributing to immune permissive tumor microenvironment.

2.3 BENEFIT/RISK ASSESSMENT

Most patients with mutations/rearrangements that confer hyperactivation of the RAS-MAPK pathway have a poor prognosis. The combination of SHP2 inhibition together with anti-PD1 inhibition provides a potentially novel targeted treatment for these patients with advanced solid

tumors harboring mutations resulting in hyperactivation of the RAS-MAPK pathway. RAS family oncogenes are frequently activated by mutations in human cancers and KRAS G12C is the predominant mutation in NSCLC (39). Therapies specifically targeting the mutant KRAS G12C, shown to be clinically effective in these previously intractable cancers. Mechanism of action and preclinical data suggest that the anticancer activity of KRAS G12C inhibitors deepened when combined with SHP2 inhibition.

SAR442720 is currently being administered to humans in a Phase 1 dose-escalation and dose-expansion monotherapy study, Protocol RMC 4630 01, (https://clinicaltrials.gov; NCT03634982) evaluating its safety, tolerability, preliminary efficacy, MTD, and RP2D, PK, and PDy profiles. More detailed information about the expected benefits and risks and reasonably expected AEs of SAR442720 based on clinical and pre-clinical data and class of drugs may be found in the SAR442720 Investigator's Brochure (IB).

Pembrolizumab is a PD-1-blocking antibody indicated for several indications including melanoma, NSCLC, Head and Neck Squamous Cell Cancer (HNSCC), Classical Hodgkin Lymphoma (cHL), Primary Mediastinal Large B-Cell Lymphoma (PMBCL), Urothelial Carcinoma, Microsatellite Instability-High Cancer, Gastric Cancer, Cervical Cancer, Hepatocellular Carcinoma (HCC), Merkel Cell Carcinoma (MCC), Renal Cell Carcinoma (RCC). Pembrolizumab has been administered in clinical trials as a single-agent and in combination with a variety of compounds and therapies. Further information can be found in the current version of the pembrolizumab US package insert.

The Phase 2 part of the adagrasib clinical study 849-001 is evaluating the clinical activity of MRTX849 in cohorts of patients who have tumors with the KRAS G12C mutation. As of 30 August 2020, clinical activity data have been reported for patients with NSCLC administered MRTX849 at the Phase 2 dose of 600 mg BID in Phase 1/1b or Phase 2 cohorts.

2.3.1 Risk assessment

2.3.1.1 Potential risks of SAR442720

Given the limited clinical experience to date, the potential risks are based on the combinations of emerging clinical safety data, pre-clinical data and class effects. Until the cut-off date of the most recent IB (17-July-2021), cumulatively 242 participants have been exposed to the drug, 113 participants in the monotherapy trial (RMC 4630-01), 112 participants in the RMC 4630-02 (cobimetinib and osimertinib combination study) and 17 participants in the pembrolizumab study (TCD16210). Based on the emerging safety data in the aforementioned studies, especially data coming from the monotherapy trial, the following potential risks have been identified: edema, diarrhea, anemia and thrombocytopenia, which are summarized in Table 11.

Most AEs observed in RMC-4630-01, RMC-4630-02, and TCD16210 are low grade in severity, primarily Grade 1 or 2, and are managed adequately in the clinic.

The safety and tolerability profiles of SAR442720 were consistent with the mechanism of action and RAS pathway inhibition. Frequently reported treatment-emergent AEs of any grade regardless of relationship to study drug by PT or group of clinically associated PTs included edema includes hemodynamic edema, effusions, and fluid overload events (48.7%), diarrhea (48.7%), anemia and fatigue, and thrombocytopenia (32.7% each), dyspnea (31.9%), nausea (21.2%), and aspartate aminotransferase increase (20.4%). Grade ≥3 TEAEs by PT or group of clinically associated PTs included anemia (16.8%), thrombocytopenia (15.0%), dyspnea (12.4%), edema (9.7%), and pneumonia (6.7%). The most frequently reported treatment-related AEs, as assessed by the Investigator, of any grade, by PT or group of clinically associated PTs were diarrhea (35.4%), thrombocytopenia (30.1%), edema (28.3%), fatigue (28.3%), and anemia (27.4%). Grade ≥3 related AEs reported included thrombocytopenia (13.3%), anemia (11.5%), hypertension and diarrhea (4.4% each). Data on the intermittent schedule suggest that it may be better tolerated than the daily schedule. For further detailed safety profile and incidence of TEAEs please refer to the most recent IB.

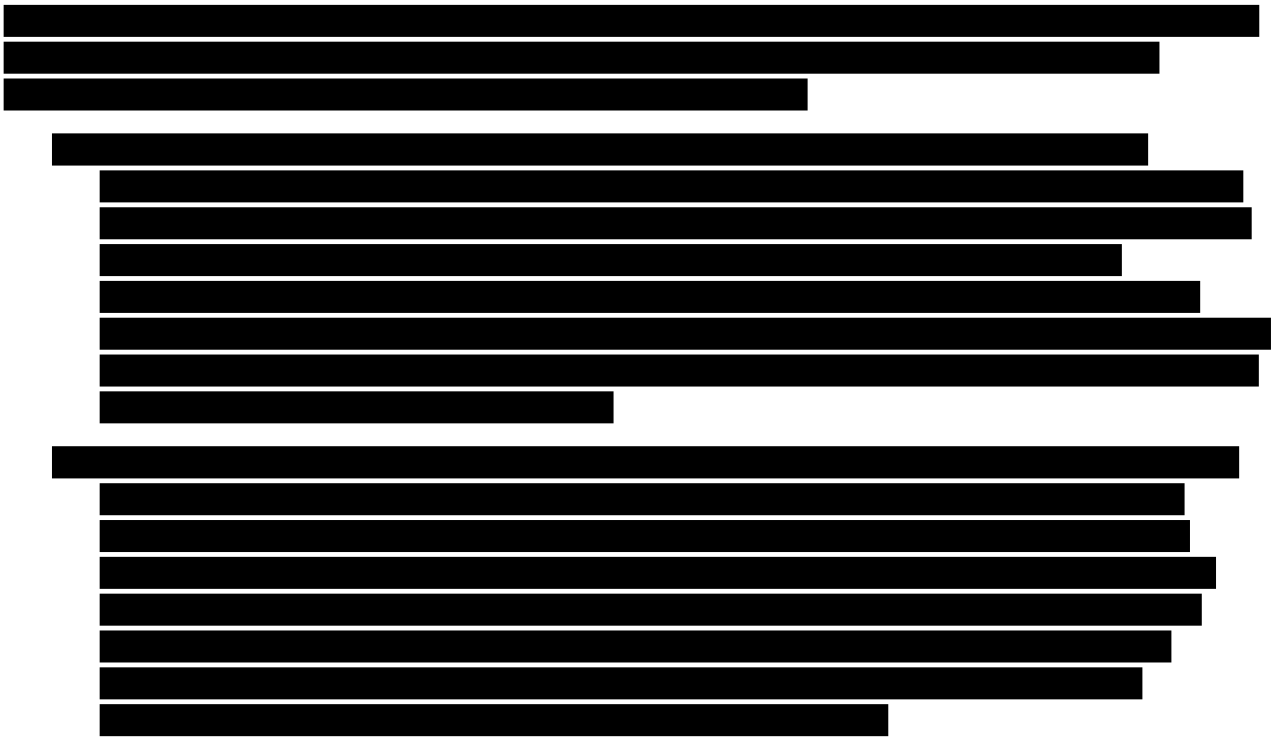
Potential risks of SAR442720 have been determined based on the emerging clinical safety data and are listed in Table 11. Amongst the potential risks associated with SAR442720, diarrhea is managed using Imodium and Lomotil in the majority of participants, thrombocytopenia is primarily managed with dose interruptions, Grade 3 anemia is managed with blood transfusions with or without dose interruptions, and edema is managed with diuretics such as Lasix or spironolactone.

Table 11 - Potential risks of SAR442720

Potential Risk	Descriptions and Guidance for the Investigator
Edema*	Edema of any grade was reported in 48.7% (55/113) of participants in study RMC-4630-01. Grade ≥3 edema was reported in 11 participants (9.7%) in study RMC-4630-01. The median time to first onset of edema was 17 days, with a median duration of 14.5 days for the resolved events. **Guidance to the Investigators:** Observe for early signs of edema and investigate for potential other clinical causes including medications. Follow institutional guidelines to manage edema including cessation of other medications known to be associated with the development of edema, if clinically indicated. Follow protocol dose modification guidelines in the event of observing edema.
Thrombocytopenia*	Thrombocytopenia AEs, of any grade, were reported in all dosing cohorts, including RP2DS of 200 mg (D1D2) in RMC-4630-01 study. The overall incidence was 33% (37/113) including 15.0% (17/113) Grade 3-4 events. No Grade 3-4 bleeding events in conjunction with thrombocytopenia have been reported as of data cutoff date. Median time to onset of thrombocytopenia** was 15 days from the start of study treatment and median duration was 24.0 days. **Guidance to the Investigators:** These recommendations refer only to the management of uncomplicated thrombocytopenia, ie, decrease in platelet counts without any accompanying clinical events of bleeding/significant bruising or other known risk factors for bleeding. For Grade 1-2 events (platelet level 50 000 to <100 000 [entry criteria]), continue treatment at current dose level and frequency and monitor closely. For Grade 3-4 events (platelet level <50 000), manage per institutional guidelines and interrupt dosing until patient recovers to Grade 1 or better (platelet level >75 000). If recovery occurs, the Investigator may resume dosing at the same dose level and frequency, if clinically appropriate. If Grade 3-4 events recur, hold dose until recovery to Grade 1 or better and consider re-introducing study drug at reduced frequency, or withdrawing patient from study therapy. For thrombocytopenia associated bleeding event or in participants with significant additional risk factors for bleeding, the general dose modification guidelines should be considered. The Investigator may interrupt or discontinue study treatment as deemed medically appropriate.
Diarrhea	Diarrhea AEs, of any grade, were reported in 48.7% (55/113) participants in the RMC-4630-01 study. Grade ≥3 AEs were reported in 5.3% (6/113) participants. Median time to onset of diarrhea was 9.0 days from the start of study treatment and median duration was 4.0 days. **Guidance to the Investigators:** Evaluate for other or concomitant causes, including medications (eg, stool softeners, laxatives, antacids), infection including Clostridium difficile, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber. For Grade 1 or 2 diarrhea, dietary modifications should be considered including cessation of lactose-containing products, eats small meals, and adequate hydration. Consumption of the BRAT (banana, rice, apples, toast) diet may be helpful. In addition, loperamide or codeine may be used or alternatives in refractory cases such as octreotide and budesonide. For >Grade 2 diarrhea, consider hospitalization for fluid and electrolyte replacement and antibiotics, particularly if accompanied by fever or Grade 3-4 neutropenia. Consultation with a gastroenterologist should be considered, particularly for severe or refractory events.
Anemia*	Anemia AEs of any grade were reported in 37.2% (42/113) participants in the RMC-4630-01 study. Grade ≥3 AEs were reported in 16.8% (19/113) participants. Median time for onset of anemia*** was 21.5 days and median duration was 21.5 days. **Guidance to the Investigators:** Monitor closely and provide supportive care according to institutional standards. Interrupt study treatment as clinically appropriate. Dose interruption or discontinuation may not be required depending on baseline hemoglobin and transfusion history.

.* Includes edema peripheral, pleural effusion, periorbital edema, face edema, pericardial effusion, localized edema, peripheral swelling, ascites, generalized edema, eyelid edema, fluid retention, joint swelling, lip edema, and pulmonary edema; thrombocytopenia includes thrombocytopenia and platelet count decreased, anemia includes anemia, anemia macrocytic, hemoglobin decreased, and normocytic anemia
** Time to and duration of thrombocytopenia was calculated using laboratory data.
*** Time to and duration of anemia was calculated using laboratory data.

Thromboembolic events:



- There was one participant (1/17) who experienced a Grade 3 pulmonary embolism in the TCD16210 study (pembrolizumab combination study, in the 200 mg cohort) approximately 40 days after the start of study medication, which was assessed as related to SAR442720.

The thromboembolic reports were heavily confounded by pre-existing risk factors and thrombosis is a known risk with higher incidence in cancer participants. Lung cancer participants may be at particularly high risk as 9/14 monotherapy participants and 5/9 SAR442720-cobimetanib arm participants with a thromboembolic event had NSCLC.

Pneumonitis:

Several drug-induced pneumonitis (including two fatal) cases have been reported in study RMC-4630-02 with cobimetinib and osimertinib combination regimens. Drug-induced pneumonitis is a known risk for both cobimetinib and osimertinib according to their labels. Pneumonitis was reported for adagrasib during clinical studies; however, there is not sufficient data to support a relationship at this time. Similarly, SAR442720 monotherapy is not associated with a higher risk of pneumonitis, whereas pembrolizumab may be associated with rare events of drug-induced pneumonitis therefore the Investigators should make all efforts to exclude pneumonitis/interstitial lung disease in case of respiratory symptoms (please refer to the IB for more details on the incidence of pneumonitis in each study).

Reactivation of autoimmune disorders is a possible adverse reaction given the published preclinical study reports that show SHP2 can bind to phosphorylated immunoreceptor tyrosine based inhibition and activation motifs (ITIM and ITAM) domains on immune regulatory receptors and SHP2 can transduce signals downstream of PD-1 (40, 41, 42, 43, 44). As such, an exclusion criterion around patient history of prior autoimmune disease has been included for Part-1 and Part-2.

[redacted] Soft tissue mineralization is considered clinically monitorable with calcium and phosphate levels since the increase in inorganic phosphorous levels precedes the soft tissue mineralization as published (45).

[redacted]

[redacted]

From non-clinical studies, SAR442720 is considered non-mutagenic, non-clastogenic/aneugenic, and non-phototoxic.

[redacted]

Please refer to the SAR442720 IB for more details regarding the safety profile.

2.3.1.2 Potential risks of pembrolizumab

Pembrolizumab is a PD-1 blocking antibody indicated in more than 12 different tumors and lines of treatment (including NSCLC and CRC).

The Warning and precautions for pembrolizumab include immune-mediated reactions which may be severe or fatal, can occur in any organ system or tissue, including the following:

immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions including Stevens Johnson syndrome and toxic epidermal necrolysis and solid organ transplant rejection. It includes infusion related reaction, embryofetal toxicity and complications of allogeneic hematopoietic stem cell transplantation (HSCT). Treatment of patients with multiple myeloma (MM) with a PD-1 or PD-L1 in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

The most common adverse reactions (reported in ≥20% of patients) are for pembrolizumab as single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. For pembrolizumab in combination with chemotherapy are: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, and peripheral neuropathy and for pembrolizumab in combination with axitinib are: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation.

Pembrolizumab has been approved for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications. Based on the modeling of dose/exposure efficacy and safety relationships and observed pharmacokinetic data from an interim analysis of 41 patients with melanoma treated with pembrolizumab 400 mg every 6 weeks, there are no anticipated clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.

Refer to Pembrolizumab US Package Insert and summary of product characteristics (SmPC) for details and the most recent information.

2.3.1.3 Potential risks of SAR442720 and pembrolizumab administration

The individual drugs have distinct mechanisms of action and safety profiles. Based on the available pre-clinical and clinical data from each individual drug, no potentially overlapping serious adverse drug reactions are anticipated with the SAR442720 and pembrolizumab combination. There is a possibility that combination of the two drugs can potentiate or alleviate the side effects that has been observed individually in monotherapy. There is also a possibility of new safety issues which are distinct from the known safety profiles of each individual drug.

The potential of drug-drug interaction between SAR442720 and pembrolizumab is low. Given pembrolizumab is a therapeutic monoclonal antibody, it is expected to be catabolized into amino acids by general protein degradation process, which is not expected to be affected by SAR442720. As pembrolizumab is not considered a cytokine modulator, it is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction, thus PK of SAR442720 is not expected to be affected by pembrolizumab as well.

2.3.1.4 Potential risks of adagrasib

Adagrasib is being evaluated as monotherapy and in combination with selected cancer therapies in various clinical studies.

As of 27-November-2020, a total of 439 subjects, including 259 patients and 180 other subjects (healthy volunteers or special populations), have been treated with adagrasib. Among enrolled patients, 67% had a primary diagnosis of NSCLC, and 20% had a primary diagnosis of CRC. A total of 202 (78%) treated patients received MRTX849 as monotherapy, while 57 (22%) patients received adagrasib in combination with another agent.

The most commonly reported TEAEs attributed to adagrasib by the investigator across all patients (irrespective of causality to any combination agents) were nausea (49.4%), diarrhea (49.0%), vomiting (36.7%), fatigue (27.8%), alanine aminotransferase (ALT) increased (16.2%),AST increased (14.7%), blood creatinine increased (12.7%), decreased appetite (12.4%), and ECG QT prolonged (10.8%).

The most commonly reported treatment-emergent SAEs of any cause reported in patient trials of adagrasib include pneumonia (4.6%), dyspnea (3.5%), hyponatremia (3.1%), malignant neoplasm progression (2.7%), dehydration (2.3%), lung infection (2.3%), acute kidney injury (1.9%), anemia (1.9%), blood creatinine increased (1.9%), hypoxia (1.9%), pleural effusion (1.9%), hypotension (1.5%), muscular weakness (1.5%), nausea (1.5%), pulmonary embolism (1.5%), pyrexia (1.5%), sepsis (1.5%), and vomiting (1.5%).Apart from the above listed common AEs, pneumonitis was reported for adagrasib during clinical studies, however there is not sufficient data to support relationship at this time.

Please refer to adagrasib IB for more details regarding the safety profile.

2.3.1.5 Potential risk for SAR442720 and adagrasib administration

SAR442720 is identified as a CYP3A and P-gp substrate, with CYP3A contributing to approximately 45% of total hepatocyte metabolism. Adagrasib is a strong inhibitor of CYP3A and a weak inhibitor of P-gp, which may increase SAR22720 exposure by up to 2-fold (mainly due to CYP3A inhibition). Starting dose of SAR442720 was reduced to 50% of its RP2D from monotherapy and Part-1 of this study. In addition, adagrasib will be started at the lower dose (400 mg BID rather than 600 mg RP2D).

SAR442720 is not anticipated to alter the PK of adagrasib, because SAR442720 has no effect on CYPs and transporters. Overlapping toxicities such as gastrointestinal toxicities are anticipated between the 2 drugs, hence such toxicities may occur more frequently than in the monotherapy settings. It is not known whether QT prolongation may occur more frequently with the combination therapy, however this cannot be excluded at this stage.

2.3.2 COVID-19 risk assessment

It is not yet known whether SAR442720 will pose additional risk for patients in the context of the current COVID-19 pandemic. However, the risk of exposure to infected people cannot be completely excluded as the participants/subjects may need to expose to public area (eg, commute to the site and at the site) (Section 10.12).

Risk mitigation for COVID-19

- Continued risk monitoring before starting the study and while on study
- Sites must follow local practice in deciding if patients need to be tested for COVID-19
- Closely monitor symptom and signs for COVID-19
- Reduce the public exposure while ambulatory, as feasible

2.3.3 Benefit assessment

SHP2 is a novel mechanism and PD-1 is proven effective in many histologyies including NSCLC. Participants in late disease setting as in Part-1 with limited or not clinically meaningful treatment options can therefore potentially benefit from novel combination approaches such as the one proposed in this study.

NSCLC is a tumor types that is benefiting from ICI treatment. The compound ICI (anti-PD1) pembrolizumab to be combined with SAR442720 in this study is approved to treat various disease settings of NSCLC, and few other anti-PD1/PD-L1 (eg, nivolumab and atezolizumab) are approved for the treatment of similar disease settings of NSCLC.

The combination regimen with adagrasib proposed to be evaluated in this study protocol amendment is anticipated to bring further benefit to participants with NSCLC. The addition of SAR442720 to adagrasib may promote anti-tumor activity by inhibiting cycling to GTP-bound KRAS in both mutant and wild-type KRAS species, therefore theoretically preventing resistance.

The Phase 2 segment of Study 849-001 is evaluating the clinical activity of MRTX849 (adagrasib) in cohorts of patients having tumors with the KRAS G12C mutation. As of 30 August 2020, clinical activity data have been reported for patients with NSCLC administered MRTX849 at the Phase 2 dose of 600 mg BID in Phase 1/1b or Phase 2 cohorts.

Among patients with NSCLC with the KRAS G12C mutation with measurable disease and at least 1 on-study assessment, 23/51 patients (45%) experienced a partial response in accordance with RECIST 1.1 based on the Investigator's assessment (3). Unconfirmed responses were initially documented among 5/23 responders, all of which were confirmed during continued study treatment. The disease control rate (PR plus stable disease) was 96.1% (49/51 of patients). Based on the clinical efficacy results described above and the preclinical efficacy data described in detail in Section 2.2.6, adding SAR442720 to adagrasib treatment may further increase clinical benefit in patients with NSCLC and KRAS G12C mutation.

2.3.4 Overall benefit: risk conclusion

Overall, the anticipated benefit/risk ratio of SAR442720 in combination with either pembrolizumab or adagrasib supports the conduct of study TCD16210 in participants with advanced solid tumors.

3 OBJECTIVES AND ENDPOINTS

Table 12 - Objectives and endpoints

Part-1 Dose Escalation (SAR442720 and pembrolizumab)	
Objectives	**Endpoints**
Primary	
• To characterize the safety and tolerability of SAR442720 in combination with pembrolizumab in participants with advanced solid tumors including non-small cell lung cancer (NSCLC) who progressed on anti-PD-1/PD-L1 containing therapy and advanced CRC after progression to all standard of care (SoC) therapy.	• Incidence, nature, and severity of treatment-emergent AEs and SAEs, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 for the combination of SAR442720 and pembrolizumab.
• To define the MTD and RP2D for the combination of SAR442720 and pembrolizumab in participants with solid tumors.	• Incidence of study drug-related dose-limiting toxicities (DLTs) in Cycle 1.
Secondary	
• To assess the pharmacokinetic(s) (PK) of SAR442720 in combination with pembrolizumab, and to assess the PK of pembrolizumab in combination with SAR442720.	• Plasma concentrations of SAR442720. • Serum concentrations of pembrolizumab.
• To estimate the anti-tumor effects of SAR442720 in combination with pembrolizumab in all participants.	• Objective response rate (ORR) and duration of response (DoR) of SAR442720 and pembrolizumab in all participants. ORR of combination therapy with SAR442720 and pembrolizumab will be based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
Part-2 Dose Expansion (SAR442720 and pembrolizumab)	
Objectives	**Endpoints**
Primary	
• To determine the anti-tumor activity of SAR442720 in combination with pembrolizumab.	• Objective response rate defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR) determined by the Investigator, per RECIST v1.1.
Secondary	
• To assess the safety profile of SAR442720 when combined with pembrolizumab.	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities according to NCI CTCAE v5.0.

Objectives	Endpoints
• To assess other indicators of anti-tumor activity.	• Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first documented evidence of PR or CR determined by the Investigator per RECIST v1.1 (for NSCLC). • DoR, defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined by the Investigator per RECIST v1.1 or death from any cause, whichever occurs first. • Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months (determined by the Investigator per RECIST v1.1. • Disease control rate (DCR) including confirmed CR or PR or SD as determined by the Investigator per RECIST v1.1. • Progression free survival (PFS), defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by the Investigator as per RECIST v1.1 or death due to any cause, whichever occurs first.
• To assess the pharmacokinetic (PK) of SAR442720 in combination with pembrolizumab, and to assess the PK of pembrolizumab in combination with SAR442720.	• Plasma concentrations of SAR442720. • Serum concentration of pembrolizumab.

[redacted]

Part-3A Dose Escalation (SAR442720 and adagrasib)

Objectives	Endpoints
Primary	
• To define the MTD and RP2D for the combination of SAR442720 and adagrasib in participants with NSCLC and KRAS G12C mutation.	• Incidence of study drug-related DLTs in Cycle 1.
• To characterize the safety and tolerability of SAR442720 in combination with adagrasib in participants with NSCLC and KRAS G12C mutation	• Incidence, nature, and severity of TEAEs and SAEs, graded according to NCI CTCAEv5.0 for the combination of SAR442720 and adagrasib.
Secondary	
• To characterize the PK of SAR442720 in combination with adagrasib, and to characterize the PK of adagrasib in combination with SAR442720.	• PK parameters of SAR442720 (C_{max}, T_{max}, $AUC_{0\text{-}last}$) • PK parameters of adagrasib (C_{max}, T_{max}, $AUC_{0\text{-}last}$)
• To estimate the anti-tumor effects of SAR442720 in combination with adagrasib in all participants	• ORR and DoR of SAR442720 and adagrasib in all participants. ORR of combination therapy with SAR442720 and adagrasib will be based on RECIST v1.1.

Part-3B Dose Expansion (SAR442720 and adagrasib)

Objectives	Endpoints
Primary	
• To determine the anti-tumor activity of SAR442720 in combination with adagrasib in participants with NSCLC and KRAS G12C mutation.	• ORR defined as the proportion of participants who have a confirmed CR or PR determined by the Investigator per RECIST v1.1.
Secondary	
• To assess the safety profile of SAR442720 when combined with adagrasib in participants with NSCLC and KRAS G12C mutation.	• Incidence of TEAEs, SAEs, and laboratory abnormalities according to NCI CTCAE v5.0.
• To assess other indicators of anti-tumor activity.	• TTR defined as the time from the first administration of investigational medicinal product (IMP) to the first documented evidence of PR or CR determined by the Investigator per RECIST v1.1 (for NSCLC). • DoR, defined as the time from first documented evidence of CR or PR until PD determined by the Investigator per RECIST v1.1 or death from any cause, whichever occurs first. • CBR including confirmed CR or PR at any time or SD of at least 6 months determined by the Investigator per RECIST v1.1. • DCR including confirmed CR or PR or SD as determined by the Investigator per RECIST v1.1. • PFS, defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by the Investigator as per RECIST v1.1 or death due to any cause, whichever occurs first.
• To assess the PK of SAR442720 in combination with adagrasib, and to assess the PK of adagrasib in combination with SAR442720.	• Plasma concentrations of SAR442720 and adagrasib.

Part-3A and Part-3B (SAR442720 and adagrasib)	
Objectives	**Endpoints**
[redacted]	

Part-4 (SAR442720 and pembrolizumab)	
Objectives	**Endpoints**
Primary	
• To evaluate the impact of food on the PK of SAR442720 when dosed in combination with pembrolizumab.	• Plasma PK parameters of SAR442720 following oral administration of SA442720 tablets in combination with pembrolizumab under fed and fasted states (eg, C_{max}, T_{max}, $AUC_{0\text{-last}}$).
• To evaluate the impact of the formulation (tablets vs. capsules) on the PK of SAR442720 when dosed in combination with pembrolizumab.	• Plasma PK parameters of SAR442720 following oral administration of SAR442720 tablets (test formulation) and capsules (reference formulation) in combination with pembrolizumab under fasted state (eg, C_{max}, T_{max}, $AUC_{0\text{-last}}$).
Secondary	
• To assess the safety and tolerability of SAR442720 under fasted and fed conditions in combination with pembrolizumab through the cycles, when dosing with capsule and tablet formulations in combination with pembrolizumab.	• Incidence, nature, and severity of TEAEs and SAEs, graded according to the NCI CTCAE v5.0 for SAR442720 in combination with pembrolizumab.
• To estimate the anti-tumor effects of SAR442720 in combination with pembrolizumab in all participants.	• ORR and DoR of SAR442720 and pembrolizumab in all participants. ORR of combination therapy with SAR442720 and pembrolizumab will be based on RECIST v1.1.

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety measurements used in this study are standard for the evaluation of therapy in participants with advanced solid tumors.

4 STUDY DESIGN

This is a Phase 1/2 open-label, multi-center, safety, preliminary efficacy, and PK study of SAR442720 in combination with other agents in participants with advanced malignancies.

4.1 OVERALL DESIGN

Part-1

Part-1 of the study is to characterize the safety and tolerability of SAR442720 in combination with pembrolizumab and to confirm the RP2D. Participants with either NSCLC or advanced CRC will be enrolled in the study. There is no minimum participant number requirement for either tumor type.

Prior to enrollment, all participants will undergo screening to determine study eligibility. Questions regarding eligible mutations may be addressed to the Sponsor. Information on tumor genotype will be collected on all participants. Participants must have one or more of the following molecular aberrations:

- *KRAS*^{G12C} mutations (NSCLC, CRC and any other histotype)
- *KRAS*^{G12A}, *KRAS*^{G12D}, *KRAS*^{G12S}, *KRAS*^{G12V} mutations (NSCLC)
- *KRAS*^{G12A}, *KRAS*^{G12D}, *KRAS*^{G12S}, *KRAS*^{G12V} and/or MSI-H or dMMR (CRC)
- *KRAS* amplification (any histotype)
- *NF1 LOF* (any histotype)
- *BRAF* Class 3 mutations (any histotype)

The presence of one or more of these tumor genotypes is required for enrollment. Eligibility will be assessed based on prior genomic testing using a clinically validated or qualified assay of tumor samples. Circulating tumor DNA (ctDNA) mutational analysis using a clinically qualified or validated test may also be used for enrollment. All local tumor genotyping analyses will be confirmed by central testing when tumor tissue is provided. A fresh biopsy will not be used to determine eligibility.

The starting DL1 of SAR442720 is 140 mg Day 1 and Day 4 BIW with pembrolizumab given at 200 mg IV Q3W. During the study, alternative BIW dose schedules, such as Day 1 and Day 2 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study can be explored after agreement of the Study Committee. The dose of SAR442720 will be escalated or de-escalated depending on the emerging safety data of the combination. The starting DL1 of SAR442720 (140 mg BIW) and DL2 (200 mg BIW) have been cleared in the ongoing Phase 1 monotherapy escalation study (https://clinicaltrials.gov; NCT03634982), and DL-1 (100 mg BIW) is 50% of the highest cleared dose in the ongoing Phase 1 monotherapy escalation study (Table 13). One of the BIW dose schedules will be tested, based on the safety and tolerability data from the ongoing Phase 1 monotherapy escalation study. The decision to initiate alternative dose levels will be made by the Study Committee after careful

evaluation of safety and/or PK data from the ongoing Phase 1 monotherapy escalation study and data generated in this combination study. Overall safety monitoring will be performed throughout the conduct of the study. Additional dose levels and/or additional schedules of administration could be tested based on emerging PK and safety data.

The DLT observation period is 1 cycle (21 days). All the AEs occurring during treatment, unless due to disease progression or to a cause obviously unrelated to IMP, will be taken into consideration by the Sponsor and recruiting Investigators for the determination of the MTD and RP2D for the SAR442720 and pembrolizumab combination. The Study Committee will review the overall safety, PK/PD and activity data and will decide the recommended dose for the expansion phase.

The Study Committee will be comprised of the Principal Investigator from each site involved in the dose escalation phase, clinical team members from the Sponsor (including at least the Study Medical Manager, Global Study Manager, and experts including the Global Safety Officer, pharmacokineticists, and biostatisticians).

The Study Committee will review clinical data on a regular basis, with a review being performed at least at the end of each DL cohort, before the enrollment of new participants at the next DL, and at the end of the dose escalation phase of the study. The Study Committee in agreement with the Sponsor's Study Medical Manager will decide on whether to escalate or de-escalate to the next DL or to add alternative dose levels during Study Committee meetings based on current safety profile and tolerability, available PK information, and statistical design recommendation. Decisions regarding participant treatment and cohort expansion will be discussed and clearly documented in the discussion minutes. The Study Committee in agreement with the Sponsor's Study Medical Manager may permit the evaluation of additional dose levels and/or additional schedules of administration of SAR442720, depending upon the observed safety and DLT at each DL, and the safety and/or PK data observed in the ongoing Phase 1 monotherapy escalation study.

Table 13 - Dose escalation for Part-1

Dose Level (DL)	SAR442720	Pembrolizumab
DL1	140 mg BIW	200 mg Q3W
DL2	200 mg BIW	200 mg Q3W
DL-1	100 mg BIW	200 mg Q3W

Abbreviations: BIW = Day 1 and Day 2 of each week, Day 1 and Day 4 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study; Q3W = once every 3 weeks

The MTD will be identified based on safety data during the DLT assessment period (Cycle 1). The RP2D will be based on all available safety, PK, PDy, and efficacy data for all treated participants.

Participants enrolled in the study will undergo regular safety assessments including physical examinations and testing as outlined in Section 8.2.1. Imaging studies (eg, computed tomography [CT] or magnetic resonance imaging [MRI]) will be performed at baseline and every 2 cycles through Cycle 6 and then every 3 cycles to assess for tumor response as per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Peripheral blood samples will be collected within Cycles 1, 2, 6 and at EOT for PK evaluation (Section 8.5). Pharmacodynamic biomarker assessments will be evaluated in peripheral blood and tumor samples (Section 8.6).

The first cycle (eg, 21 days) constitutes the DLT assessment period. The first participant in the initial combination dose level will be observed for the first 7 days of dosing prior to dosing additional participants in this cohort. Following this 7-day observation period, additional participants may be enrolled in the cohort. In subsequent combination dose level cohorts, participants may be enrolled concurrently.

Part-2

The expansion cohort (Part-2), un-controlled, non-randomized, open-label will assess the anti-tumor activity and safety of SAR442720 combined with pembrolizumab in participants with lung cancer.

Part-2 will assess the anti-tumor efficacy and safety of adding SAR442720 to therapeutic approaches with documented efficacy profile as 1L NSCLC therapy.

- Cohort A1: participants with PD-L1 TPS ≥50% NSCLC to receive SAR442720 + pembrolizumab as 1L therapy.
- Cohort A2: participants with PD-L1 TPS 1%-49% NSCLC to receive SAR442720 + pembrolizumab as 1L therapy.

Part-2 of the study will start once RP2D for SAR442720 from Part-1 is confirmed. The SAR442720 RP2D will be 200 mg BIW, Day 1 and Day 2 of each week, administered orally (21 days per cycle). This dose emerged as the safe dose of SAR442720 from the escalation part (Part-1) of this study. Pembrolizumab will be administered as a dose of 200 mg using a 30 minutes IV infusion on Day 1 every 3 weeks (21 days cycle) or a dose of 400 mg using a 30 minutes IV infusion on Day 1 every 6 weeks (42 days cycle).

The duration of the study for a participant will include:

- Screening period: up to 28 days.
- Treatment Period: enrolled participants will receive continuous treatment until PD, unacceptable AE, other full permanent discontinuation criteria as described in Section 7.1.
- End of Treatment and Follow-up: EOT visit will occur 30 days ±5 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the Observation period and will be followed differently depending on the reason leading to EOT:

- Participants who discontinue study treatment with radiological or clinical PD (per RECIST v1.1) or iCPD (per iRECIST) will be followed in the Follow-Up Visit 1 occurring 3 months ±5 days from last IMP administration, or until start of new anticancer therapy or cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.

Part-3

Part-3 of this open-label, multi-center, un-controlled, non-randomized study, will assess the safety, RP2D, anti-tumor activity, and PK of SAR442720 in combination with adagrasib in participants with NSCLC harboring KRAS G12C mutation.

Part-3A

SAR442720 and adagrasib will be administered orally on a continuous basis. The starting dose (DL1) of SAR442720 will be 100 mg on Day 1 and Day 2 BIW with adagrasib given at 400 mg BID orally. The dose escalation will follow the mTPI2 design with a minimum of 3 participants evaluable for DLT for each dose level. Participants will be DLT-evaluable if they have taken at least 80% of the scheduled Cycle 1 dose of both drugs in the first 21 days of treatment. The same mTPI-2 design as that used in Part-1 will be used in Part-3A.

The dose of SAR442720 will be escalated or de-escalated depending on the emerging safety data of the combination. The starting dose (dose level 1 [DL1]) of SAR442720 will be 100 mg BIW, which is 50% of the highest cleared dose in the ongoing Phase 1 monotherapy dose escalation study (https://clinicaltrials.gov; NCT03634982). DL2 (140 mg BIW) and DL 3 (200 mg BIW) for SAR442720 have been cleared in the ongoing Phase 1 monotherapy dose escalation study. The adagrasib starting dose (DL1) will be 400 mg BID orally, which is one dose level below the RP2D in monotherapy (3). Refer to Table 14 below for dose escalation. At least 6 participants need to be treated at the MTD and RP2D.

Table 14 - Dose escalation for Part-3A

Dose Level	SAR442720 (BIW)	Adagrasib (daily)
Part-3 – DL(-)1	80 mg D1, D2	400 mg BID
Part-3 – DL1 (starting dose)	100 mg D1, D2	400 mg BID
Part-3 – DL2	140 mg D1, D2	400 mg BID
Part-3 – DL3a[a]	140 mg D1, D2	600 mg BID
Part-3 – DL3b[a]	200 mg D1, D2	400 mg BID
Part-3 – DL4	200 mg D1, D2	600 mg BID

Abbreviations: BID, twice daily; BIW, twice a week; D, day; DL, dose level.
a DL3b is optional and may be recommended by the study committee according to the safety data before further escalating to DL4.

Overall safety monitoring will be performed throughout the conduct of the study. Additional dose levels and/or additional schedules of administration can be tested based on emerging PK and safety data.

The DLT observation period is 1 cycle (21 days). All the AEs occurring during treatment, unless due to disease progression or to a cause obviously unrelated to IMP, will be taken into consideration by the Sponsor and recruiting Investigators for the determination of the MTD and RP2D for the SAR442720 and adagrasib combination. The Study Committee will review the overall safety, PK/PD, and clinical activity data and in agreement with the Sponsor's Study Medical Manager, will decide the recommended dose for the expansion phase.

The Study Committee will be comprised of the Principal Investigator from each site involved in the dose escalation phase, clinical team members from the Sponsor (including at least the Study Medical Manager, Global Study Manager, and experts when appropriate such as Global Safety Officer, pharmacokineticists, and biostatisticians).

The Study Committee will review clinical data on a regular basis, with a review being performed at least at the end of each DL cohort, before the enrollment of new participants at the next DL, and at the end of the dose escalation phase of the study. The Study Committee in agreement with the Sponsor's Study Medical Manager will decide on whether to escalate or de-escalate to the next DL or to add alternative dose levels during Study Committee meetings based on current safety profile and tolerability, available PK information, and statistical design recommendation. Decisions regarding participant treatment and cohort expansion will be discussed and clearly documented in the discussion minutes. The Study Committee in agreement with the Sponsor's Study Medical Manager may permit the evaluation of additional DLs and/or additional schedules of administration of SAR442720 and adagrasib, depending upon the observed safety and DLT at each DL, and the safety and/or PK data observed in the ongoing study.

In Part-3A approximately 15 to 30 DLT evaluable participants are expected to be enrolled during the Dose Escalation. The design of the study assumes 5 combination dose levels with 3 to 6 participants per dose level.

Part-3B

The Part-3B dose expansion will assess the anti-tumor activity and safety of SAR442720 combined with adagrasib in participants with NSCLC harboring KRAS G12C mutation.

The Part-3B dose expansion of the study will start once RP2D for SAR442720 and adagrasib from the Part-3A dose escalation is confirmed.

Approximately 40 participants will be enrolled in Part-3B dose expansion and treated at the RP2D identified in Part-3A (see Section 9.2).

"Note: Enrolled participants are all participants from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not".

Part-4

The Part-4 of this Phase 1/2, open-label, multi-center, non-randomized study will assess the effect of food on the PK of SAR442720 tablet, when dosed in combination with pembrolizumab in participants with advanced malignancies. It will also evaluate the relative bioavailability of SAR442720 tablet formulation (test) compared to the SAR442720 capsule formulation (reference) when dosed in combination with pembrolizumab in participants with advanced malignancies.

SAR442720 and pembrolizumab will be administered on a continuous basis, with SAR442720 administered orally at the RP2D determined from Part-1, and pembrolizumab administered intravenously at 200 mg Q3W or 400 mg Q6W. The SAR442720 tablet formulation (test) will be administered during the first cycle (21 days), and starting from C2D1, SAR442720 capsule formulation (reference) will be administered until the EOT. On C1D1, each participant will receive SAR442720 tablet in combination with pembrolizumab with a moderate-calorie moderate-fat breakfast after an overnight fast of 10 hours. The breakfast should be consumed within 0.5 hour, and there should be another 4 hour fast after the completion of breakfast. On C1D15, each participant will receive SAR44272 tablet in combination with pembrolizumab after a 10 hour overnight fast prior to dosing on C1D15, followed by a 4 hour fast postdose. On C2D1, each participant will receive SAR442720 capsule in combination with pembrolizumab after a 10 hour overnight fast prior to dosing on C2D1, followed by a 4 hour fast postdose. For all other days (except for C1D1, C1D15, and C2D1), participants will be fasted for 1 hour prior and 1 hour after each SAR442720 dose. Water will be permitted for participants in either fasted or fed state, except for 1 hour before and 1 hour after the administration of SAR442720. Participants will be instructed to take SAR442720 with 240 mL of water. The menu options for the fed cohort are shown in Appendix 13 (Section 10.13). The timing of sample collection for PK of SA4442720 and pembrolizumab is presented in Table 8. In Part-4, up to approximately 12 participants are expected to be enrolled.

4.1.1 Dose-limiting toxicity criteria (Part-1 and Part-3A)

Potential DLTs are defined as all AEs specified below occurring during the first cycle of treatment considered by the investigator to be related to study treatment, unless due to disease progression or to a cause obviously unrelated to IMP.

- Grade ≥4 AEs.
- Grade 3 neutropenia lasting >7 days or febrile neutropenia.
- Grade 3 thrombocytopenia with clinically significant bleeding.
- Any Grade ≥3 immune-related AEs (irAE) (Part-1, 2, and 4 only).

  An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.
- Grade 3 nonhematologic AEs, including rash, nausea/vomiting, hypertension, diarrhea, retinopathy, or blurred vision that remain uncontrolled (does not resolve to ≤ Grade 2) for >72 hours despite maximal supportive care. Electrolyte abnormalities or Grade 3 asymptomatic creatine phosphokinase (CPK) or gamma-glutamyl transferase (GGT) elevations that are corrected within 72 hours will not be considered DLTs.
- Grade 3AST, ALT, and/or total bilirubin elevations that persist >5 days.

- Concurrent elevation of AST or ALT >3 × upper limit of normal (ULN) and total bilirubin >2 × ULN or international normalized ratio (INR) >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (possible Hy's law case).
- Grade 3 QTcF (defined as QT interval corrected using Fridericia's formula [QTcF] >450 msec or change from baseline of QTcF >50 msec) prolongation.
- Retinal vein occlusion (RVO) any grade
- Toxicity related to IMP leading to 50% or less dose intensity of SAR442720 (eg, miss ≥3 doses) and/or delay in initiation of Cycle 2 dosing of pembrolizumab by >15 days, in the absence of recovery to baseline or Grade ≤1 (except for alopecia, vitiligo, fatigue and thyroiditis) AE. Toxicity resulting in the inability to deliver at least 66.7% of the dose of adagrasib (Part-3A) as intended for the duration of the cycle.
- An absolute decrease in LVEF of 20 percentage points or greater from the baseline value to a value that is below the institutional lower limit of normal (LLN) value, OR symptomatic systolic dysfunction with LVEF decrease from baseline ≥10% and/or below LLN.

At the end of Cycle 1, each participant must be assessed by the Investigator to determine if he or she experienced a DLT. This information must be recorded on the appropriate electronic case report forms (eCRFs), and an electronic DLT notification (either DLT or not) will be sent to the Sponsor, before a subsequent cycle may begin.

Potential and IMP related DLTs will be considered as AESIs. As such, Investigators are required to report them to the Sponsor within 24 hours of the Investigator becoming aware of each AE. The Investigator will attach the DLT-specific case report form (CRF) page to the transmitted DLT/AESI form or will complete the specific DLT form in the eCRF.

The reported potential DLTs will be reviewed by the Sponsor and recruiting Investigators in order to determine their relationship to the IMP and confirm them as DLTs.

4.1.2 Dose escalation

In Part-1 and Part-3A, dose escalation will follow mTPI2 design with a minimum of 3 participants evaluable for DLT in the first cycle. A participant will be considered evaluable for DLT assessment if he/she receives at least 4 out of the 6 planned doses of SAR442720 in the first cycle and completes the DLT observation period or if he/she experiences a DLT in the DLT observation period. A participant who is not DLT-evaluable will be replaced to achieve a minimum of 3 DLT-evaluable participants at the same cohort.

The actual dose selected at each dose escalation decision, and the MTD identified at the conclusion of the dose escalation phase, will be determined by the Study Committee, in agreement with the Sponsor's Study Medical Manager, which may select a dose at or below the model's recommendation and should not select a dose that is suggested to be over toxic by the model. The Study Committee will review the overall safety of all dose levels. More details in the model and its operating characteristics can be found in Appendix 11 (Section 10.11).

The adaptive dose escalation design is based on the boundaries generated from the mTPI2 design. The dose escalation will stop if the next recommended dose has been collectively evaluated in at least 2 previous escalation cohorts.

It is anticipated that in Part-1 12 to 18 DLT-evaluable participants and in Part-3A 15 to 30 DLT-evaluable participants will be enrolled in the dose escalation. The actual total number of participants required will depend on the number of dose levels evaluated and on the incidence and timing of observed DLTs.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The first phase of the study (Part-1) constitutes a Dose Escalation, which has been designed to minimize the number of participants exposed to potentially subtherapeutic doses.

In the Dose Escalation, assessment of safety and tolerability will be the primary endpoints and will be directly measured by the incidence of DLTs, AEs, and SAEs. The dose escalation rationale is provided below in Section 4.2.1.

A mini-expansion cohort of 6 participants will be initiated to further assess the safety, PK, PD, as well as the preliminary anti-tumor activity of SAR442720 and pembrolizumab combination therapy at RP2D.

The Part-2 of this study aims to establish the efficacy of combining the ICI pembrolizumab with the SHP2 inhibitor SAR442720 which may result in an increase in ORR. The goal of combination therapy approaches is to expand the spectrum of patients who respond to cancer immunotherapy and to improve the quality of clinical responses (ie, durable response OS and prolonged PFS) beyond what can be achieved with monotherapy alone. The established anti-tumor activity of PD-1/PD-L1 inhibition as monotherapy in a wide spectrum of cancers coupled with its favorable toxicity profile provides a strong rationale for its use as a backbone for combinatorial strategies.

The design of the study is a non-randomized study where the experimental combination will be assessed in a single cohort for each indication. The ORR will be assessed using RECIST v1.1 for participants with NSCLC. The objective response will be assessed per Investigator in first intention. Central imaging reading may be done retrospectively if significant activity is observed.

Part-3A constitutes a dose escalation study to determine the MTD and RP2D of SAR442720 in combination with adagrasib in participants with NSCLC and KARAS G12C mutations. The starting dose of SAR442720 is 50% of the highest cleared dose in monotherapy and adagrasib starting dose is 2/3 of RP2D for adagrasib. In the dose escalation part, assessment of safety and tolerability will be the primary endpoints and will be directly measured by the incidence of DLTs, AEs, and SAEs.

Part-3B aims to determine the anti-tumor activity of SAR442720 in combination with adagrasib in participants with NSCLC and KARAS G12C mutations, which can result in an increased ORR. The goal of the combination therapy approach is to expand the spectrum of patients who respond to targeted KRAS G12C therapy and to improve the quality of clinical responses (ie, durable response and prolonged PFS) beyond what can be achieved with monotherapy alone.

The design of the study is a non-randomized study in which the experimental combination will be assessed in a single cohort for each indication. The ORR will be assessed using RECIST v1.1. The objective response will be assessed by the Investigator in first intention. Central imaging reading may be done retrospectively if significant activity is observed.

Part-4 aims to assess the impact of formulation and preliminary impact of food on the PK of SAR442720 in combination with pembrolizumab. Part-4 is an open label, non-randomized fixed-sequence study, intending to assess preliminary effect of food on SAR442720 tablet and relative bioavailability of SAR442720 tablets versus capsules in participants with advanced malignancies. The PK of SAR442720 under fasted state will be served as the test treatment of formulation bridging; therefore, both the food effect and formulation effect can be assessed in the same participants, to reduce the number of participants needed.

4.2.1 Dose escalation rationale

The mTPI2 design is a Bayesian interval design that can be implemented in a simple fashion as the traditional 3+3 design, but it is more flexible and possesses superior operating characteristics. The mTPI2 design provides an upgrade to the modified toxicity probability interval (mTPI) design, with a substantially lower risk of overdosing and a better precision to identify the MTD. The mTPI2 design is applicable for the dose escalations in Part-1 and Part-3A.

The target toxicity rate for the MTD is [redacted], with the acceptable toxicity probability interval of [redacted]. At least 3 DLT evaluable participants will be included in each cohort. The decision by the Study Committee in agreement with the Sponsor's Study Medical Manager for dose escalation/de-escalation or stay will be made after the completion of the first cycle of the last DLT evaluable participant at each cohort. The mTPI2 decision rules are based on calculating the unit probability mass (UPM) of intervals as follows:[redacted] Intervals that are lower than[redacted] indicating dose escalation, equivalence interval[redacted]indicating staying at the current dose level, and intervals that are higher than[redacted] indicating dose de-escalation. The interval with the largest UPM will be the winning interval and implies the corresponding dose recommendation. The detailed mTPI2 rules are displayed in Table 15.

When using Table 15, note the following:

A) If the next dose level is considered to have unacceptable high toxicity, ie, the probability that the DLT rate is larger than [redacted] at the next dose is more than[redacted], then the next enrolled cohort should be kept at current dose and the higher dose will never be used (Decision "DU" in Table 15).

B) At any time, if the observed DLT rate at the current dose level is greater than[redacted], then the next enrolled cohort should be de-escalated to the lower dose level, at which the DLT rate is less than [redacted].

C) If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new participants at the lowest dose unless there is unacceptable high toxicity, at which point terminate the study for safety. If the decision based on the new cohort at the lowest dose still recommends dose de-escalation, new dose levels may be explored.

D) If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose. If the decision based on the new cohort at the highest dose still recommends dose escalation, new dose levels may be explored.

E) If at least 6 participants were treated at the recommended dose level, then this dose level will be the MTD.

F) Skipping dose is not allowed.

Table 15 - Dose escalation rule of the modified toxicity probability interval-2 method

		Number of participants treated at current dose								
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Number of dose-limiting toxicities	**0**	E	E	E	E	E	E	E	E	E
	1	D	D	S	S	E	E	E	E	E
	2		DU	D[a]	D	D	S	S	S	E
	3			DU	DU	D	D	D	D	S
	4				DU	DU	DU	D	D	D
	5					DU	DU	DU	DU	DU
	6						DU	DU	DU	DU
	7							DU	DU	DU
	8								DU	DU
	9									DU

E: Escalate to the next higher dose, S: Stay at the current dose, D: De-escalate to the next lower dose, DU: De-escalate to the next lower dose and the current dose will never be used again because unacceptable high toxicity

a "D" will not be applied for first cohort of dose level 1 as the exception, however "DU" will give priority to the exception, ie, if 3 out of 3 participants have DLT at the dose level 1, the study committee may add lower dose level to assess the safety.

4.3 JUSTIFICATION FOR DOSE

Part-1 (SAR442720)

The starting dose of SAR442720 is selected based on ongoing clinical trials. The starting dose of SAR442720 is 140 mg Day 1 and Day 4 BIW, [redacted]Please refer to RMC 4630 IB for more details. Given the overall safety profile based on the available clinical data on pembrolizumab and SAR442720 monotherapy, the starting dose of SAR442720 in this combination study is 140 mg administered orally BIW (Day 1 and Day 4 schedule) in a 21-day cycle. During the study, alternative BIW dose schedules, such as Day 1 and Day 2 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study can be explored after agreement of the Study Committee.

Part-2 (SAR442720)

Part-2 of the study will start once RP2D for SAR442720 from Part-1 is confirmed. The dose of SAR442720 in Part-2 will be the RP2D, which will be the highest cleared dose from Part-1 which will most likely be 200 mg BIW, such as D1 and D2 of each week.

The dose of pembrolizumab for Part-1 and Part-2 is the fixed recommended dose of 200 mg IV Q3W or 400 mg IV Q6W.

Part-3 (SAR442720 and adagrasib)

The starting dose of SAR442720 is selected based on the preliminary clinical safety and tolerability observed in Phase 1 RMC-4630-01 monotherapy study. A dose of 200 mg BIW Day 1 Day 2 SAR442720 has been cleared by the Dose Committee and selected as the RP2D for the final expansion cohort. SAR442720 is identified as a CYP3A and P-gp substrate, with CYP3A contributing to approximately [redacted] of total hepatocyte metabolism. Adagrasib is a strong inhibitor of CYP3A and a weak inhibitor of P-gp, which may increase SAR442720 exposure up to [redacted] (mainly due to CYP3A inhibition). Therefore, the starting dose of SAR442720 is selected to be [redacted] less than the RP2D at monotherapy, which is 100 mg Day 1, Day 2 (D1D2).

SAR442720 is not anticipated to alter the PK of adagrasib.

Part-4 (SAR442720)

Part-4 of the study will start at the RP2D for SAR442720 from Part-1, the highest cleared dose from Part-1, which is 200 mg BIW, administered on D1 and D2 of each week. This dose has been cleared by the Dose Committee and selected as the RP2D for the combination of SAR442720 and pembrolizumab.

The dose of pembrolizumab for Part-4 is the fixed recommended dose of 200 mg IV Q3W or 400 mg IV Q6W.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

I 01. All participants must be ≥18 years of age (or country's legal age of majority if >18 years), at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Part-1 and Part-4 participants should have histologically or cytologically proven diagnosis of non-squamous NSCLC with metastatic disease progression after platinum-based chemotherapy and ICI irrespective of the sequence, ie, either concurrently or sequentially:

- At least one prior line of treatment in a metastatic setting
- Relapse to develop metastatic disease during or within 6 months of an adjuvant/neoadjuvant treatment (to be considered as first-line treatment), OR
- Disease progression after or during one platinum-based chemotherapy and one ICI (anti-PD1/PD-L1) irrespective of the sequence, ie, concurrently or sequentially.

OR

Histologically proven diagnosis of advanced solid tumors including CRC that have failed, are intolerant to or are considered ineligible for SoC anti-cancer treatments including approved drugs for oncogenic drivers in their tumor type.

I 03. Part-1 participants must have one or more of the following molecular aberrations:

- $KRAS^{G12C}$ mutations (NSCLC, CRC and any other histotype)
- $KRAS^{G12A}$, $KRAS^{G12D}$, $KRAS^{G12S}$, $KRAS^{G12V}$ mutations (NSCLC)
- $KRAS^{G12A}$, $KRAS^{G12D}$, $KRAS^{G12S}$, $KRAS^{G12V}$ and/or MSI-H or dMMR (CRC)
- KRAS amplification (any histotype)
- NF1 LOF (any histotype)
- BRAF Class 3 mutations (any histotype)

I 04. All participants should have at least 1 measurable disease per RECIST v1.1. An irradiated lesion can be considered measurable only if progression has been demonstrated on the irradiated lesion.

I 05. All participants should have Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

Sex

I 06. All (male or female) participants

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

A male participant must agree to use contraception (see Appendix 4 [Section 10.4]) during the intervention period and for at least 4 months (6 months for Part-3) after the last dose of study intervention.

b) Female participants

A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 [Section 10.4]).

  OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 [Section 10.4]) during the intervention period and for at least 4 months (6 months for Part-3) after the last dose of study intervention.

Informed Consent

I 07. All participants should be capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Part-2 (new criteria added with amendment 03)

I 08. Cancer diagnosis at study entry:

For participants in Cohorts A, - histologically or cytologically confirmed diagnosis of Stage IV (per American Joint Committee on Cancer [AJCC] 8th edition [112]) NSCLC.

I 09. For Part-2, PD-L1 expression TPS as determined (with an absolute value provided to Sponsor) at local laboratory.

- Cohort A1: PD-L1 expression TPS ≥50%,
- Cohort A2: PD-L1 expression TPS 1%-49%.

I 10. Provision of tumor tissue:

- Mandatory for participants enrolled with local PD-L1 testing. Baseline tumor tissue or slides should be provided for central lab retrospective analysis. Archival tumor tissue samples should be obtained from biopsies done within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment. Slides specifications are detailed in Lab Manual.

I 11. Prior anticancer therapy

- For participants in Cohorts A1 and A2 - Have not received prior systemic therapy for advanced/metastatic NSCLC. Participants who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 6 months prior to the development of metastatic disease.

Part-3 (new criteria added with amendment 04)

I 12. Participants with histologically or cytologically proven metastatic NSCLC with at least one prior line of treatment in a metastatic setting. Prior KRAS G12C targeted therapy is acceptable (only in Part-3A)

I 13. Participants must have following molecular aberration tested at the local laboratory:

- KRAS G12C mutation assessed by a local Sponsor-approved test. Approved test list can be found in eCRF.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Predicted life expectancy ≤3 months.

E 02. Primary central nervous system (CNS) tumors.

E 03. Known or suspected leptomeningeal or brain metastases, symptomatic or impending spinal cord compression. Participants previously treated for these conditions who have had stable CNS disease (eg, no evidence of clinical and radiographic disease progression and asymptomatic in the absence of corticosteroids or anti-convulsant therapy over the previous 4 weeks) are eligible.

E 04. History of cerebrovascular stroke or transient ischemic attack within previous 6 months.

E 05. Prior solid organ or hematologic transplant.

E 06. The following ocular abnormalities are excluded:

a) History or current retinal pigment epithelial detachment (RPED), central serous retinopathy, RVO, neovascular macular degeneration, or factors considered by the Investigator to present an unacceptable risk of RPED or RVO.

b) Visible retinal pathology as assessed on ophthalmic examination that is considered a significant risk factor for RVO or RPED by an ophthalmologist.

E 07. Any of the following cardiovascular abnormalities:

a) Symptomatic congestive heart failure, New York Heart Association Class II or higher

b) Acute coronary syndrome (eg, unstable angina, coronary artery stenting, or angioplasty, bypass grafting) within prior 6 months

c) History or current uncontrolled clinically significant unstable arrhythmias

d) Participants who have pacemakers to control atrial arrhythmias are candidates for the study. Participants with medically controlled atrial fibrillation >6 months prior to C1D1 are eligible.

e) History of congenital long QT syndrome or prolonged QTcF interval >480 msec using Fridericia's formula (unless a pacemaker is in place) or uncorrectable abnormalities in blood electrolytes (sodium, potassium, calcium, magnesium, phosphorus).

f) Left ventricular ejection fraction (LVEF) < institutional LLN or <50%, whichever is lower.

E 08. Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-PD 1/PD-L1 agents and anti-CTLA 4 monoclonal antibodies) that caused permanent discontinuation of the agent, or that were Grade 3 or 4 in severity, or that have not resolved to baseline at least 3 months prior to initiation of IMP. For other agents, treatment related immune mediated (or immune related) AEs that were Grade 2 or above (applies to Part-1, Part-2, and Part-4).

E 09. Ongoing AEs (excluding alopecia and fatigue) caused by any prior anti-cancer therapy ≥ Grade 2 (NCI-CTCAE Version 5.0).

E 10. Active, known or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except for replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement) (applies to Part-1, Part-2 and Part-4).

E 11. History of or current interstitial lung disease, active pneumonitis, or pneumonitis that requires oral or IV glucocorticoids to assist with management (radiation pneumonitis in the radiation field is permitted; radiation pneumonitis that requires steroids is not permitted); history of thoracic radiation therapy of >30 Gy within 6 months of the first dose of trial treatment.

E 12. Receipt of a live-virus vaccination within 28 days of planned treatment start. Receipt of viral vaccine that do not contain live virus within 7 days. Seasonal flu vaccines that do not contain live virus are permitted.

E 13. Known infection with human immunodeficiency virus (HIV), known uncontrolled hepatitis B virus (HBV) infection, known uncontrolled hepatitis-C virus (HCV) infection, active tuberculosis, or severe infection requiring parenteral antibiotic treatment. To control HBV infection, participants with positive hepatitis B surface antigen (HBsAg) should have started anti-HBV therapy before initiation of IMP, and the screening HBV viral load should be <2000 IU/mL (104 copies/mL). The anti-HBV therapy should continue throughout the treatment period. The HCV-treated participants must have completed their treatment at least 1 month prior to starting study intervention. Participants with positive HCV antibody and undetectable HCV RNA without anti-HCV therapy are eligible.

E 14. Known second malignancy either progressing or requiring active treatment within the last 3 years (except for basal cell carcinoma of the skin, squamous cell carcinoma of the skin, ductal carcinoma in situ (DCIS) of the breast, or in situ cervical cancer that has undergone potentially curative therapy).

E 15. Impairment of gastrointestinal function that may alter the absorption of SAR442720 (eg, uncontrolled nausea and vomiting, diarrhea, malabsorption syndrome, inflammatory bowel disease, gastrectomy, small bowel resection).

E 16. History of severe allergic reaction to any of the study intervention components.

Prior/concomitant therapy

E 17. Last administration of prior anti-tumor therapy (chemotherapy, targeted agents, and immunotherapy) or any investigational treatment within 28 days or less than 5 times the half-lives of the agent (whichever is shorter) prior to the first dose of IMP.

E 18. Participant who has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

E 19. Comorbidity requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of IMP initiation. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder.

E 20. Major surgery ≤28 days or non-study related minor procedures (eg, Port-a-Cath placement) ≤7 days prior to C1D1. In all cases, the participant must be sufficiently recovered and stable before treatment administration.

E 21. Any other unstable or clinically significant concurrent medical condition (eg, substance abuse, uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism, etc) that would, in the opinion of the investigator, jeopardize the safety of a participant, impact their expected survival through the end of the study participation, and/or impact their ability to comply with the protocol.

E 22. Medication and supplements that may interfere or potentiate with SAR442720 and/or adagrasib metabolism or toxicity PRIOR or DURING study intervention are excluded:

- Strong CYP3A4 inducers or inhibitors (within 7 days prior)
- Strong P-glycoprotein (P-gp) inhibitors (eg, cyclosporine, tacrolimus; within 7 days prior)
- Strong Breast Cancer Resistance Protein (BCRP) inhibitors (eg, eltrombopag; within 7 days prior) (applies to Part-3 only)
- Proton pump inhibitors (within 3 days prior) or H2-receptor antagonists (within 1 day prior) during the dose escalation portion of the study
- Medications known to prolong QTc interval
- Acetylsalicylic acid (low dose aspirin, anticoagulation with low-molecular weight heparin or direct Factor X inhibitors and LMWH are allowed. Prophylactic LMWH is also allowed for high risk patients with hypercoagulability).

Diagnostic assessments

E 23. Inadequate organ and bone marrow function at the Screening visit:

- Absolute neutrophil count (ANC) <1000 μ/L (1×10^9/L).
- Platelets $<100 \times 10^3$ μ/L (after at least 3 days without platelet transfusion).
- Hemoglobin <9 g/dL or <5.6 mmol/L (without transfusions within 2 weeks of initiation of IMP).
- Total bilirubin >2 × ULN.
- AST and/or ALT >3 × ULN (or >5 × ULN for participants with liver metastases).
- Blood creatinine >1.5 × ULN or creatinine clearance of <50 mL/min (using Cockcroft Gault formula or 24-hour urine collection)
- Prothrombin time (PT)/international normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT/PTT) >1.3 × ULN or outside the therapeutic range of the local laboratory if receiving therapeutic anticoagulation that would affect the PT/INR.

Other exclusions

E 24. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 25. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 26. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) Ordinance E6).

E 27. Any specific situation during study implementation/course that may rise ethics considerations.

E 28. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

Tumor characteristics for Part-2, Part-3, and Part-4 (new criteria added with amendment 03):

E 29. Following known genotypes are excluded for expansion cohorts:

a) NRAS (except G12A/C)

b) RASQ61

c) KRASG13

d) BRAF Class 1, 2, or unclassified

e) PIK3CA

New criteria added with amendment 04

E 30. Subject has a known activating SHP2 mutation (eg, Noonan syndrome)

E 31. Treatment with following agents in Part-3 only:

- KRAS G12C inhibitors (Part-3B only)
- SHP2 inhibitors (Part-3B only)
- CYP3A substrates with a narrow therapeutic index

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

1. Refrain from consumption of grapefruit or grapefruit containing products, or Seville oranges from 7 days before the start of study intervention until after the final dose.
2. Fasting (except water) 1 hour prior to and 1 hour after each SAR442720 dose is required. On days when both medications are administered together, fasting is requisite due to the requirements of SAR442720. For participants in Part-3, adagrasib may be taken with or without food. When co-administered with SAR442720, adagrasib should be taken without food (as SAR442720 requirement). For participants enrolled in Part-4, meal consumptions will be based on the protocol instructions. Vegan and non-vegan meals are defined in the protocol and are comparable in terms of kilocalories as well as fat consumption and similar to classic meals in terms of fed conditions (non-vegan meals will be provided except for patients who are vegans). Please see Appendix 13 (Section 10.13).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently able to receive treatment in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (ie, screen failure) may be rescreened without a new ICF if within 5 days of the initial screening date of screen failure. Rescreened participants should be assigned the same participant number as for the initial screening, if within 5 days of initial screening. Only hematology, chemistry, and coagulation tests may need to be repeated if outside the screening window. Other clinical testing will not need to be repeated if outside screening window (ie, within 5 days).

6 STUDY INTERVENTION

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 16 - Overview of study interventions administered in Part-1, -2, and -4

Study Intervention name	**SAR442720**		**Pembrolizumab**
Type	Drug		
Dose formulation	Powder-in-capsule	Film-coated tablet	Lyophilized powder in single-dose vial for reconstitution or solution in a single-dose vial
Unit dose strengths	20 mg and 100 mg		50 mg/vial or 100 mg/4 mL (25 mg/mL)
Dosage levels	The starting dose depends on which combination is evaluated		200 mg Q3W or 400 mg Q6W (for Part-2)
Route of administration	Oral with water after 1 hour fast; no food or drink (other than water) allowed for 1 hour after administration		Intravenous infusion over 30 minutes in accordance with the product leaflet
Use	Experimental combination		
IMP and NIMP	IMP		
Packaging and labeling	SAR442720 capsule will be provided in 8-count HDPE bottles	SAR442720 tablets will be provided in a wallet containing 1 Aclar blister of 8 tablets	Pembrolizumab will be provided in 50 mg lyophilized powder in single-dose vial for reconstitution or 100 mg/4 mL (25 mg/mL) solution in a single-dose vial
	Each bottle will be labeled as required per country requirement	Each wallet will be labeled as required per country requirements	Each box will be labeled as required per country requirement
Current/Former names or aliases	SAR442720, RMC-4630, RMC 0694630	SAR442720	KEYTRUDA®, pembrolizumab

Abbreviation: BID = twice daily; BIW = Day 1 and Day 2 of each week, Day 1 and Day 4 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study; HDPE, high-density polyethylene, IMP, investigational medical product; NIMP, noninvestigational medical product; Q3W = once every 3 weeks; Q6W, Q3W = once every 3 weeks.

Table 17 - Overview of study interventions administered in Part-3

Study Intervention name	**SAR442720**	**Adagrasib**
Type	Drugs	
Dose formulation	Powder-in-capsule	Film coated tablets
Unit dose strengths	20 mg and 100 mg	200 mg
Dosage levels	The starting dose depends on which combination is evaluated	400 mg BID or 600 mg BID; should be at 12-hour intervals to the extent possible
Route of administration	Oral with water after 1 hour fast; no food or drink (other than water) allowed for 1 hour after administration	Oral with at least 240 mL (8 ounces) of water; may be taken with or without food
Use	Experimental combination	
IMP and NIMP	IMP	
Packaging and labeling	SAR442720 capsule will be provided in 8-count HDPE bottles Each bottle will be labeled as required per country requirements	Adagrasib tablets will be provided in 132-count HDPE bottles Each bottle will be labeled as required per country requirements
Current/Former names or aliases	SAR442720, RMC-4630, RMC 0694630	MRTX849, adagrasib

Abbreviation: BID = twice daily; HDPE, high-density polyethylene, IMP, investigational medical product; NIMP, noninvestigational medical product.

6.1.1 Investigational medicinal product

The number of SAR442720 20 mg and 100 mg bottles and adagrasib 200 mg bottles will be dispensed depending on the dose level and will cover the treatment until the next dispensation visit.

When applicable, pembrolizumab will be sourced from available commercial supplies. Otherwise it will be relabeled by the Sponsor as per country requirements and according to Good Manufacturing Practice (GMP) guidelines.

Further details on IMPs will be described in the Pharmacy Manual.

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, SAR442720 20 mg and 100 mg bottles and adagrasib 200 mg bottles may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant (Direct-To-Patient [DTP] process).

6.1.2 Non-investigational medicinal product

Appropriate premedication for study treatments may be administered at the Investigator's discretion according to the usual clinical practice and in accordance with institutional guidelines. If premedication is required, all the drugs used will also be entered to the concomitant medication pages.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

SAR442720 (powder-in-capsule drug products: 20 mg and 100 mg) is stored as following: Store below 30°C (86°F). Do not freeze.

SAR442720 (aclar/aluminum blister tablets: 20 mg and 100 mg) is stored as follows: Store between 2°C and 30°C (36°F to 86°F). Do not freeze.

Pembrolizumab is stored as follows:

- Lyophilized powder: Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).
- Solution: Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Adagrasib is stored as follows:

- MRTX849 tablets are provided in single bottles (no cartons) and should be stored at room temperature (2°C to 25°C, 36°F to 77°F) according to the instructions on the label.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open label study without randomization. No blinding or randomization will be used for this study. In order to minimize bias, the participants will be assigned sequentially as they are enrolled into the study using the inclusion and exclusion criteria as outlined in Section 5.1 and Section 5.2. Enrollment will be confirmed by the sponsor Medical Monitor after review of all supporting documentation for eligibility criteria.

Participants will be allocated a screening number at the time of signing the ICF. If a participant is a screen failure, the number will not be reassigned.

6.4 STUDY INTERVENTION COMPLIANCE

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules and checking the participant diary information during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of SAR442720 capsules, SAR442720 tablets, and adagrasib tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be collected and recorded in eCRF.

6.4.1 Missed dose

SAR442720: If a participant misses a dose, it may be taken at the time the omission was discovered as long as it is within 24 hours of the original administration time. Otherwise, the dose should not be administered and should be recorded as an omission. The participant should not administer more than the recommended dose.

Adagrasib: If a dose is inadvertently missed, the dose should be skipped if >4 hours has elapsed since the expected dosing time. Dosing may resume at the next schedule time.

6.5 CONCOMITANT THERAPY

Supportive care (eg, antiemetics, analgesics, blood transfusions, hematopoietic growth factor support) may be used at the investigator's discretion and in accordance with institutional procedures. Localized radiotherapy used for palliative purposes may be considered after discussion with the Medical Monitor. Low dose aspirin and anticoagulation with low-molecular weight heparin or direct Factor X inhibitors and LMWH are allowed. Prophylactic LMWH is also allowed for high risk patients with hypercoagulability. Contraceptives are also allowed throughout the study as described in Appendix 4 (Section 10.4).

Antacids are permitted but should not be consumed within 3 to 4 hours before or after SAR442720 administration.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Route of administration

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

6.5.1 Prohibited concomitant therapy

In addition to prohibited medications/foods listed in Exclusion Criteria (Section 5.2), a complete list of prohibited medications during study treatment is provided in Appendix 10 (Section 10.10).

The following medications are prohibited while on study treatment:

- Medications known to prolong QTc interval
- Anti-cancer therapy (except SAR442720 and pembrolizumab or adagrasib)
- Strong CYP3A4 inhibitors and inducers
- Strong P-gp inhibitors
- Strong BCRP inhibitors (Part-3 only)
- CYP3A substrates with a narrow therapeutic index (Part-3 only)

- Proton pump inhibitors (only during the dose escalation portion of the study; for Part-3 during both escalation and expansion).
- H2-receptor antagonists (only during the dose escalation portion of the study). H2-receptor antagonist can be given at least 2 hours before and 10 hours after adagrasib (Part-3 only).
- Acetylsalicylic acid (low dose aspirin and anticoagulation with low-molecular weight heparin or direct Factor X inhibitors and LMWH are allowed. Prophylactic LMWH is also allowed for high risk patients with hypercoagulability).

6.6 DOSE MODIFICATION

A 21-day cycle will be maintained, and dose interruption will be noted in the 21-day cycle schedule.

In the Dose Escalation cohorts, there will be no dose reductions or modifications during C1, 21-day DLT assessment period unless a DLT has occurred. After Cycle 1 and in the final dose cohort, if a dose reduction is recommended, then the SAR442720 dose level should be the previous lower dose level considered to be tolerable in prior participants receiving that dose. Two dose reductions are allowed.

In Part-2, dose reduction will be allowed for SAR442720 according to the criteria detailed below. SAR442720 may be reduced to the dose corresponding to one dose level below RP2D. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

In Part-3, dose reduction for SAR442720 will be as described below. SAR442720 may be reduced to the dose corresponding to one dose level below.

In Part-4, dose reduction of SAR442720 is not allowed on C1D1, C1D15, and C2D1. For other doses, dose reduction or interruption may be allowed. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

Two types of dose modifications are allowed, “dose interruption” and “dose level reduction” according to the dose modification criteria and guidelines outlined in Section 6.6.1 below. Any allowed dose modification and any deviation from the intended dose (missed doses or overdoses due to participant error) should be documented on the dose eCRF.

6.6.1 Dose modification criteria

6.6.1.1 General guidelines for adagrasib (Part-3)

The following are the general guidelines for withholding, resumption or re-challenge of treatment with adagrasib:

- following adagrasib dose reduction and control of an AE, re-challenge at a higher adagrasib dose may be permitted after discussion with the Sponsor;

- if resumption of dosing for adagrasib is delayed for ≥14 days due to an AE that is at least suspected to be attributable to study treatment, then resumption at a reduced dose should be considered;

- if treatment with adagrasib is withheld for ≥22 consecutive days, then permanent discontinuation from treatment with one or both agents should be considered; and

- if a treatment-related AE recurs despite dose reduction of adagrasib to the lowest dose anticipated, then permanent discontinuation from study treatment should be considered, unless after discussion with the Sponsor it is considered to be in the best interest of the participant to continue.

Treatment interruptions and modification guidelines are provided in Appendix 9 (Section 10.9).

Additional guidelines for adagrasib:

Hepatic Toxicities

Hepatic toxicities that are considered to be causally related to adagrasib should initially be managed with treatment interruption of one or both study drugs as outlined in Table 27. Evaluations for confounding factors (eg, cholestasis, metastasis, or viral infection) should be performed as clinically indicated, and more frequent monitoring of a hepatic panel (including AST, ALT, alkaline phosphatase, and bilirubin) should be considered for those participants with transaminase increases. Following resolution of toxicity to the specified degree, dose reduction of adagrasib should be implemented.

Other Laboratory Investigation-Based Toxicities

Other laboratory investigation-based toxicities that are considered to be causally related to adagrasib should initially be managed with treatment interruption of adagrasib as outlined in Table 27. Following resolution of toxicity to the specified degree, dose reduction of adagrasib should be implemented.

Cardiac Toxicities

Cardiac toxicities that are considered to be causally related to adagrasib should initially be managed with treatment interruption of adagrasib as outlined in Table 27. Cardiology consultation should be obtained for cases of QTcF prolongation or LVEF decreases falling into the categories indicated in Table 27. In addition, more frequent monitoring of electrolytes that include potassium and magnesium should be considered for participants with vomiting, diarrhea, or past instances of hypokalemia or hypomagnesemia that could recur, and oral and/or intravenous supplementation should be considered for levels below the lower limit of normal. Additionally, arrhythmia should be included in the differential diagnosis of relevant AEs (eg, palpitations, syncope, pre-syncope, or unexplained dyspnea), and unscheduled ECGs should be performed for participants with such events or electrolyte abnormalities as clinically indicated. Additional assessments of LVEF should be performed as clinically indicated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

Following resolution of toxicity to the specified degree, dose reduction of adagrasib should be implemented.

Pneumonitis

Pneumonitis has been reported in the Phase 1 study of adagrasib. An evaluation should be performed to assess the attribution of pneumonitis to adagrasib. Pneumonitis considered to be causally related to adagrasib should be initially managed with treatment interruption of adagrasib as outlined in Table 27. Following resolution of toxicity to the specified degree, dose reduction of adagrasib should be implemented.

Other Toxicities

Other toxicities that are considered to be causally related to adagrasib should initially be managed with treatment interruption as outlined in Table 27. Following resolution of toxicity to the specified degree, dose reduction of adagrasib should be implemented.

Hormonal Contraceptives and Thrombotic Events

In female participants using hormonal contraceptives, the potential exists for adagrasib to inhibit hepatic cytochrome P450 and CYP3A4 and increase exposure to hormonal contraceptive levels, with the associated risk of venous thromboembolism (e.g., deep vein thrombosis or pulmonary embolism). Precautions should be taken in participants with recent, clinically significant thrombotic events, and all participants using hormonal contraceptives should be closely monitored for emerging signs of thrombotic events. Treatment with adagrasib should be interrupted in participants with signs or symptoms of thrombosis and permanently discontinued in participants who develop clinically significant thromboembolic complications. If in the judgment of the Investigator resumption of treatment with adagrasib is in the best interest of the participant, concomitant treatment with hormonal contraceptives should be discontinued.

6.6.1.2 Management of diarrhea

Evaluate for other or concomitant causes, including medications (eg, stool softeners, laxatives, antacids), infection including *Clostridium difficile*, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber.

For Grade 1 or 2 diarrhea, dietary modifications should be considered including cessation of lactose-containing products, eat small meals, and adequate hydration. Consumption of the BRAT (banana, rice, apples, toast) diet may be helpful. In addition, loperamide or diphenoxylate/atropine, or codeine may be used or alternatives in refractory cases such as octreotide and budesonide.

For > Grade 2 diarrhea, consider hospitalization for fluid and electrolyte replacement and antibiotics, particularly if accompanied by fever or Grade 3 to 4 neutropenia.

Please refer to Table 27 for dose modifications guidelines. For immune related colitis, defer to institutional guidelines.

Consultation with a gastroenterologist should be considered, particularly for severe or refractory cases.

6.6.1.3 Management of ophthalmologic complications

The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. Immediate consultation should be sought for Grade >1 visual changes. Special attention should be given to retinal (eg, central serous retinopathy [CSR]) or retinal vein abnormalities (eg, RVO). If consultation cannot be obtained within 7 days of onset, interrupt treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib) until the consultation has occurred.

If RVO is diagnosed, permanently discontinue treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib) immediately and treat per institutional guidelines. If uveitis is diagnosed, withhold treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib) and consider use of topical steroids until resolution. If CSR or neurosensory retinal detachment is diagnosed, withhold treatment until symptoms resolve and retinal exam shows resolution. Restart medication(s) at one dose level lower and close monitoring following re-initiation of medication(s). If > Grade 1 symptoms recur or follow-up ophthalmology examination worsens, withhold treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib) and either further decrease the dose or permanently discontinue treatment.

6.6.1.4 Management of hypertension

Early identification and treatment of hypertension is recommended. Evaluate for other or concomitant causes. Assess renal function as well as urinalysis. For recurrent or persistent hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) treat according to institutional guidelines with the goal of therapy to reduce blood pressure to <140 mmHg systolic/90 mmHg diastolic. Hypertension associated with life-threatening consequences (eg, malignant hypertension, neurological deficits, hypertensive crisis), permanently discontinue treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib).

Please refer to Table 27 for dose modifications guidelines. Cardiology or nephrology consultation should be considered, as clinically indicated.

6.6.1.5 Management of rhabdomyolysis or symptomatic CPK increase

Assess for other causes of CPK elevation and rhabdomyolysis such as strenuous exercise, trauma, heat-related causes, ischemia, inflammatory process, etc. For CPK elevations, rule out cardiac causes by obtaining ECG, cardiac troponin, and CK-MB fraction. Evaluate for rhabdomyolysis and potential renal compromise with a clinical examination, urinalysis, and complete blood chemistry (eg, metabolic panel). Treat according to institutional guidelines. Early IV hydration with urine alkalization provided that there are no contraindications. Nephrology consultation should be considered, as clinically indicated.

6.6.1.6 Management of liver function abnormalities and hepatotoxicity

Assess whether metastatic disease to the liver is contributing to liver function abnormalities and/or hepatotoxicity. Evaluate for infections or other causes of increased liver function abnormalities if appropriate. Consider imaging of the liver. Hold or dose reduce concomitant medications which may potentiate hepatotoxicity or metabolized by the liver. Evaluate extent of liver injury (eg, albumin level, PTT, INR) and if there is evidence of severe injury, then discontinue treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib).

Please refer to Table 27 for dose modifications guidelines for LFTs.

6.6.1.7 Management of decrease in left ventricular ejection fraction

Asymptomatic absolute decrease in LVEF from baseline ≥20% from baseline and below LLN, withhold treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib) for up to 4 weeks and repeat echocardiogram (ECHO) for LVEF at 2, 4, 10, and 16 weeks after treatment was withheld. Restart at reduced dose if LVEF ≥LLN and absolute decrease from baseline LVEF <20%. Permanently discontinue if symptoms if symptoms of heart failure are present.

Symptomatic reduction: In case of symptomatic systolic dysfunction with an LVEF decrease from baseline ≥10% and/or below LLN, withhold both SAR442720 and pembrolizumab for up to 4 weeks and consider permanent discontinuation if considered causative; in Part-3 permanently discontinue SAR442720 and adagrasib.

Please refer to Table 27 for dose modifications guidelines. Cardiology consultation should be considered.

6.6.1.8 Management of hemorrhage

Evaluate complete blood count and coagulation laboratories. Transfuse blood products and correct coagulation abnormalities as per institutional guidelines. Withhold treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib) if hemorrhage associated with thrombocytopenia, reduced platelet count from baseline, or at the discretion of investigator.

Please refer to Table 27 for dose modifications guidelines.

6.6.1.9 Management of pyrexia

Evaluate for source of fever. Obtain a complete blood count (CBC). Routine infectious work-up and treatment with antibiotics may not be necessary for participants with uncomplicated pyrexia without localizing symptoms; but work-up may be completed and antibiotic may be given, based on the clinical assessment. Hold pembrolizumab until fever resolves and restart with same dose and schedule. SAR442720 or adagrasib may be held at the investigator's discretion. Antipyretics may be given for treatment or as prophylaxis in participants with recurrent pyrexia associated with a medication. Consider short-course of low-dose corticosteroids for recurrent/recalcitrant fevers. Evaluation blood chemistry (ie, renal function test) for those with severe pyrexia.

6.6.1.10 Management of fatigue

Other causes of fatigue should be evaluated (eg, infection, disease progression and hematological, electrolyte, heart failure and endocrine abnormalities). Dose-modification and/or low-dose corticosteroids may be considered.

6.6.1.11 Pneumonitis

Respiratory symptoms such as cough, shortness of breath, etc. should be investigated with a chest X-ray or chest CT scan. Evaluate for possible infections and other causes of respiratory compromise including progressive pulmonary disease, cardiac dysfunction, etc.

6.6.1.12 Management of edema

Evaluate for other or concomitant causes including medications. Treat according to institutional guidelines including the cessation of other medications known to be associated with the development of edema, if clinically indicated.

6.6.1.13 Management of rash

For macular/papular rash or perifollicular eruptions, emollients alone may be used for Grade 1 AEs. For Grade 2 AEs, addition of antihistamines and/or topical corticosteroids are recommended. For Grade >2 events, oral steroids may be required.

For dry skin, alcohol-free emollients and soap substitutes should be considered. For folliculitis or cysts, soap substitutes and topical or oral antibiotics are recommended. Consider surgical excision for symptomatic, uninfected cysts. For an erythema-nodosum type rash, emollients, topical steroids and analgesics are recommended. In more severe cases, dermatologic evaluation and systemic steroids may be required.

Please refer to Table 27 for dose modifications guidelines. Consultation with a dermatologist should be considered as clinically indicated, including worsening or refractory symptoms, or rapidly growing lesions.

6.7 INTERVENTION AFTER THE END OF THE STUDY

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SOA) for the last participant in the trial globally.

The participant’s treatment after the end of the study will be at discretion of treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for 30 days. See the schedule of activities (SoA; Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcF) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Participants may stop study therapy yet continue to be monitored in the study under the following circumstances:

- A participant who experiences a Grade 4 AE, including those that meet the criteria of a DLT (ie, during Cycle 1), but is deemed by the investigator not to meet the criteria for withdrawal from the study (see below).
- Prolonged QTcF >450 msec OR change from baseline of QTcF >50 msec and that does not resolve after excluding other causes.

A participant must be discontinued from protocol prescribed therapy and removed from the study if any of the following apply:

- Documented disease progression based on RECIST v1.1
  - In certain circumstances (eg, an isolated site of progression with responses at other sites that may be amenable to localized radiotherapy), participants may be allowed to continue therapy during and after radiation with approval from sponsor Medical Monitor.
- Significant AEs leading to discontinuation of study medications
- Death
- Participant’s request to withdraw from study treatment
- Ineligibility
- Unwillingness or inability to comply with study requirements
- Initiation of alternative anticancer therapy

- Investigator's decision
  - Clinical need for concomitant or other ancillary therapy that is not permitted in the study
  - Unrelated intercurrent illness that, in the judgment of the investigator, will affect assessments of clinical status to a significant degree
  - Investigator believes that it is in the best interest of the participant to withdraw from the study
- Pregnancy
- Lost to follow-up
- Sponsor's decision to terminate the study

Participants who have stable disease as best response will be allowed to continue on treatment provided the investigator believes it is in the participant's best interest and none of the above criteria have been met.

During the conduct of the study, in cases where premature discontinuation of SAR442720 is required, the participant may continue pembrolizumab or adagrasib treatment, upon Investigator decision and in agreement with the Study Medical Manager. Likewise, in cases where premature discontinuation of pembrolizumab or adagrasib is required, the participant may continue SAR442720 treatment if there is presence of, or potential for, clinical benefit as assessed by the Investigator and Study Medical Manager.

Participants who discontinue study treatment should complete the safety follow up or EOT visit, within 30 days after the last treatment dose. Participants who do not withdraw consent will also undergo long term follow up until death or end of study or lost to follow-up.

Refer to SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a PK sample, if appropriate.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs as described in Section 6.6 or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (eg, COVID-19) (Section 10.12). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant may be withdrawn from the study for any of the following reasons:

- Participant's withdrawal of consent for participation in the study
- Sponsor's decision to terminate the study
- Participant is lost to follow up
- Death

If study discontinuation occurs at the same time as treatment discontinuation, every effort should be made to complete the safety follow up or EOT visit, within 30 days after the last treatment dose. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Participants who do not withdraw consent will also undergo a long term follow up for survival (SoA in Section 1.3).

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). 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 specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.9).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential 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, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

Participants will be assessed for response using RECIST v1.1 (Appendix 7 [Section 10.7]) as assessed by the investigator. All measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator based on physical examination (including measurement of cutaneous lesions) and CT scans or MRI. Imaging should include chest and abdomen (neck and pelvis are to be included depending on primary tumor type and investigator assessment). At the investigator's discretion, the imaging studies may be repeated at any time if disease progression is suspected. Additional studies, such as positron emission tomography (PET) scans, should be performed if clinically indicated. Care should be taken to repeat the same modality used at screening throughout the study and to ensure all anatomy imaged at screening is again imaged at follow up scans for any given participant. As part of the tumor assessment, physical examinations should include all areas of tumor involvement that are amenable to examination, including biopsy sites, lymph nodes, and bone tenderness, if applicable.

All imaging studies should be evaluated by a local radiologist with expertise in the imaging modality. The investigator is responsible for determining the overall response at each time point.

In Part-1 and Part-4, the first response assessment will occur after completion of C2 (C3D1 ± 7 days). Subsequent response assessments will occur every 2 cycles through the end of C6 (C7D1 ± 7 days) and then every 3 cycles.

In Part-2, the assessment of anti-tumor activity documented by objective response to the IMP is the primary endpoint for this study and is conducted as per schedule provided in the SoA (Table 3). All participants treated must have at least one measurable lesion for inclusion. The initial tumor imaging will be performed within 28 days prior to C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (56 ±7 days) after the date of first IMP and if clinically indicated.

Imaging studies should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. CT scan/MRI of the chest, abdomen, pelvis and any other locations with suspicion or evidence of disease involvement is required for the baseline assessment. Tumor assessment is not needed for participants who start a new anticancer therapy.

In Part-3A the first response assessment will occur after completion of C2 (C3D1 ± 7 days). Subsequent response assessments will occur every 2 cycles through the end of C6 (C7D1 ± 7 days) and then every 3 cycles. In Part-3B, the assessment of anti-tumor activity documented by objective response to the IMPs is the primary endpoint for this study and will be conducted as per the schedule provided in the SoA (Table 4).

A partial or complete response must be confirmed on a second examination done at least 4 weeks apart, in order to be documented as a confirmed response to therapy.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination should be performed as described in SoA (Section 1.3). The examination should include an evaluation of the head, eyes, ears, nose, and throat (HEENT), dermatologic, cardiovascular, respiratory, GI (including assessments of liver and spleen), musculoskeletal, neurological, and lymphatic systems. As part of tumor assessment, physical examinations should include all areas of tumor involvement that are amenable to examination including sites, biopsy, lymph nodes, and bone tenderness, if applicable. A symptom/AE directed physical examination should be performed as indicated by participant presentation or reported symptoms or AEs. New or worsened abnormalities should be recorded as AEs, if appropriate.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

Vital signs will be measured after 5 to 10 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, and pulse oximetry. Results should be recorded in the CRF.

8.2.3 Weight and height

Weight should be measured throughout the study as indicated in the SoA (Section 1.3). Coats should be removed prior to measurement. Height should be measured at baseline, preferably without shoes. Abnormalities including >10% weight change, should be recorded as AEs, if appropriate.

8.2.4 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.2.5 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - 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.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.6 ECOG performance status

ECOG performance status (Appendix 8 [Section 10.8]) should be evaluated by the investigator by direct questioning of the participant at baseline and at time points throughout the study as delineated in the SoA (Section 1.3).

8.2.7 Retinal examinations

Retinal examinations performed by an ophthalmologist are required during this study as described in the SoA (Section 1.3). Examinations include best-corrected visual acuity including pinhole vision if indicated, dilated funduscopic examinations, and macular and optical coherence tomography (OCT). Additional tests, such as fluorescein angiography, may be utilized to monitor leakage and inflammation-related side effects.

Ophthalmic examination including full fundoscopic examination and OCT should be performed by an ophthalmologist. Additional examinations should be performed during study treatment as clinically indicated.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of AEs and SAEs, can be found in Appendix 3 (Section 10.3).

Adverse Events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue SAR442720 (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3).

After the signing of the ICF, but prior to initiation of study intervention, only SAEs caused by a protocol mandated intervention will be collected (eg, SAEs related to invasive procedures, such as biopsies or medication washout). Any medical occurrence that begins before the start of study intervention but after obtaining informed consent, and which is not considered an SAE caused by a protocol mandated intervention will be recorded on the Medical History/Current Medical Conditions Section of the eCRF not the AE section.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

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 occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AESIs (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE within 24 hours of first learning of the SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention 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.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB for SAR442720 and US Package insert or SmPC for pembrolizumab).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until EOT.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse event of special interest

Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor within 24 hours of first learning of the AESI is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with SAR442720 is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.
  - Infusion with pembrolizumab: increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration. Injectable administration: at least twice the dose during the planned intervals
  - An overdose (accidental or intentional) with adagrasib is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and is defined as any amount above the intended dose.
- Concurrent increase in ALT and AST >3 × ULN AND total bilirubin >2 × ULN or INR >1.5 ULN in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (possible Hy's law). Study drug should be withheld until AST, ALT, return to <2 × ULN and total bilirubin returns to <1.5 × ULN.
- **Other project specific AESI(s)**
  - QT (corrected or uncorrected) >480 msec or increased from baseline>60 msec (see Section 7.1.1 QT prolongation management advice)
  - Thrombocytopenia Grade ≥3 or any grade if associated with clinically significant bleeding (see Section 6.6.1.8 for hemorrhage management guidelines)

- Edema, including generalized/peripheral edema or facial/periorbital edema (see Section 6.6.1.12 for edema management guidelines)
- All protocol defined potential or IMP related DLTs are considered as AESI, regardless of the cycle of occurrence (ie, after Cycle 1 in both escalation and expansion phases)

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

The Sponsor does not recommend specific treatment for an overdose (defined in Section 8.3.6).

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until SAR442720 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 1 to 2 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document appropriately in the CRF.

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

8.5 PHARMACOKINETICS

Plasma samples will be obtained for PK analysis of SAR442720 as outlined in the SoA (see Section 1.3). Concentrations at each time point will be reported.

- Whole blood samples of approximately 1.5 mL will be collected and processed into plasma for measurement of plasma concentrations of SAR442720 as specified in the SoA (see Section 1.3). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of SAR442720 plasma concentration may also be used for exploratory analysis, such as metabolic profiling of SAR442720.

Serum samples will be obtained for PK analysis of pembrolizumab as outlined in the SoA (see Section 1.3). Concentrations at each time point will be reported.

- Whole blood samples of approximately 1.5 mL will be collected and processed into serum for measurement of serum concentrations of pembrolizumab as specified in the SoA (see Section 1.3). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.
- Samples collected for analyses of pembrolizumab serum concentration may also be used for other analysis, such as immunogenicity assessment.
- Plasma samples will be obtained for PK analysis of adagrasib as outlined in the SoA (see Section 1.3). Concentrations at each time point will be reported.
- Whole blood samples of approximately 1.5 mL will be collected and processed into plasma for measurement of plasma concentrations of adagrasib as specified in the SoA (see Section 1.3). Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time of each sample will be recorded.
- For Part-3A and Part-4, the PK parameters of SAR442720 and adagrasib will be calculated using a non-compartmental method. The PK parameters (eg, C_{max}, time to achieve maximum concentration [T_{max}], area under the concentration–time curve from Time 0 to Time t [AUC_{0-t}], area under the concentration–time curve from Time 0 to infinity [AUC_{inf}], elimination half-life [$t_{1/2}$], if possible, and the accumulation ratio) of SAR442720 and adagrasib will be assessed for each evaluable participant.
- PK population analysis may be conducted to obtain the PK parameters of SAR442720, pembrolizumab, and/or adagrasib. If performed, the results will be summarized in a separate report.
- Samples collected for analyses of the concentration of SAR442720, pembrolizumab, and adagrasib may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.6 PHARMACODYNAMICS

Whole blood samples will be collected throughout the study as outlined in the SoA (Section 1.3). RNA expression signatures for RAS-MAPK pathway and other relevant genes will be used to explore target engagement and pharmacodynamic (PDy) modulation in Part1 and Part2.

In Part-1, fresh tumor tissue is required for PDy biomarker analyses unless the investigator determines that the tumor site is not amenable to biopsy and poses a significant risk to participant safety. The Sponsor will evaluate this requirement on a case-by-case basis (see Section 1.3 Table 2). An EOT biopsy will be requested and is optional. Biopsies will be collected 1) prior to treatment; 2) on treatment; and 3) optional at EOT or disease progression.

In Part-2 and Part-3, baseline tumor tissue is required, on-treatment and EOT biopsy is optional (Table 3 and Table 4).

The primary purpose of the on-treatment biopsies is to assess for target inhibition by quantifying expression patterns of genes downstream of the RAS-MAPK, key immune pathways and mutational landscape. Where sufficient tumor tissue passing quality control is available, predictive biomarkers will be explored. Details on processes for collection and shipment can be found in the laboratory manual.

8.7 GENETICS

Eligible mutations will be based on prior genotyping results using a clinically validated or qualified test. This test may have been performed on either tumor tissue or ctDNA samples. Sites must provide the Sponsor with the report. Where available, archival tumor tissue will be collected for retrospective central lab testing. Where a discrepancy lies between the local and central results for the eligibility defining mutation, the participant will remain on study. For data analysis purposes, results from the central laboratory will supersede those of the local laboratory.

Fresh tumor biopsy is collected, where sufficient tissue passing QC is available, with the aim of confirming mutations identified on the genomic report provided at enrollment, assessing RAS-MAPK pathway and other gene expression patterns as a measurement of drug activity. In addition, we will use genomic data from tumor tissue to 1) define biomarkers for sensitivity, resistance, and toxicity to SAR442720 and other agents in combination and 2) to assess clonal dynamics and RNA expression changes within the tumor cell population before, during and after treatment. Blood sample at baseline will be used as germline control from consenting participants in Part-2.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

Genetic analyses will not be performed on PK samples. Participant confidentiality will be maintained. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety-monitoring scheme or amendment of the ICF.

8.8 BIOMARKERS

Blood samples will be collected as outlined in the SoA (Section 1.3) for RNA expression analysis for evaluation of RAS-MAPK gene signature and other gene expression patterns in Part-1 and Part-2 participants. The aim of this is to assess the effects of the drugs on global gene regulation.

Blood samples will be collected as outlined in the SoA (Section 1.3) for immune-phenotyping analysis to evaluate modulation of key immune cells in peripheral blood in Part-1 and Part-2.

Blood samples will be collected as outlined in the SoA (Section 1.3) for ctDNA analysis to assess temporal clonal dynamics in tumors.

Blood samples will be collected as outlines in the SoA (Section 1.3) for measurement of cytokine/soluble factors that are known to be modulated by RAS-MAPK pathway and/or may reflect changes in the immune system after exposure to SHP2 or PD-1 blockade in Part-1 and Part-2.

Special procedures for collection, handling, storage and shipment of samples for biomarker analysis will be described in a separate laboratory manual which will be available at the investigational site. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarkers related to SAR442720 and/or cancer or related diseases, or to develop methods, assays, prognostics and/or companion diagnostics, and potentially to identify new drug targets or biomarkers.

Details of sample collection, processing and logistics are described in the laboratory manual.

8.9 IMMUNOGENICITY ASSESSMENTS

Immunogenicity of pembrolizumab will not be assessed, given the fact that the incidence of anti-drug antibody (including neutralizing antibody) positivity is not comparable across studies and assays, due to several factors, including but not limited to differences in assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. Participants with positive treatment-emergent anti-pembrolizumab antibody is approximately 2% (0.5% positive neutralizing antibody) according to US Package Insert, and there was no evidence of an altered PK profile or increased infusion reactions in these participants. In addition, pembrolizumab showed flat exposure-response profile in terms of safety across a dose range of 1 to 10 mg/kg, and it is unlikely for SAR442720 to trigger additional safety concerns of pembrolizumab, due to altered immunogenicity.

As SAR442720 and adagrasib are small molecules, immunogenicity testing of SAR442720 or adagrasib is not required.

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to participants in the ICF Part-2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.7).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant’s coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary objective of Part-1 is to find the MTD and RP2D for the combination therapy of SAR442720 and pembrolizumab. In Part-2 the study is designed to assess clinical benefit of SAR442720 when combined with pembrolizumab. Similarly, Part-3 is designed to find the RP2D, explore the anti-tumor activity, and PK of SAR442720 in combination with adagrasib. Part-4 is to evaluate the effect of food and relative bioavailability of different formulations. Therefore, there is no formal statistical hypothesis and testing procedure defined in this study.

9.2 SAMPLE SIZE DETERMINATION

The sample size is not calculated from statistical consideration since there will not be any formal statistical test performed. Overall, up to 134 participants will be enrolled.

In Part-1, at least 6 participants need to be treated at the MTD. After MTD is identified, another 6 participants will be treated at the MTD to confirm the decision and determine the RP2D. Therefore, a range of 18 to 24 DLT-evaluable (defined in Section 9.3) participants will be enrolled in the Part-1 of this study. The actual sample size will vary depending on DLTs observed and the number of dose levels explored.

In Part-2, 40 participants, including 20 participants in Cohort A1 with PD-L1 TPS ≥50% and 20 participants in Cohort A2 with PD-L1 TPS in 1-49%, will be enrolled at the RP2D identified from Part-1. Table 18 lists estimated ORR and the corresponding 90% exact CIs by number of responders in Part-2.

Table 18 - Estimated objective response rate (ORR) and 90% CI in Part-2

Number of responders (N=20)	ORR	90% CI for ORR (Clopper-Pearson)
4	20%	(7.1%, 40.1%)
5	25%	(10.4%, 45.6%)
6	30%	(14.0%, 50.8%)
7	35%	(17.7%, 55.8%)
9	45%	(25.9%, 65.3%)
11	55%	(34.7%, 74.1%)
12	60%	(39.4%, 78.3%)

With a sample size of 20 study participants in each cohort of Part-2, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 18.2%, 33.2%, or 64.2%, respectively.

In Part-3A, a range of approximately 15 to 30 DLT-evaluable (defined in Section 9.3) participants will be enrolled in this study. The actual sample size will vary depending on DLTs observed and the number of dose levels explored.

In Part-3B, approximately 40 participants will be enrolled at the RP2D identified from Part-3A. Table 19 lists the estimated ORR and the corresponding 90% exact CIs by the number of responders in Part-3B.

Table 19 - Estimated objective response rate (ORR) and 90% CI in Part-3B

Number of responders (N=40)	ORR	90% CI for ORR (Clopper-Pearson)
13	32.5%	(20.4%, 46.6%)
15	37.5%	(24.7%, 51.7%)
17	42.5%	(29.2%, 56.7%)
19	47.5%	(33.8%, 61.5%)
21	52.5%	(38.5%, 66.2%)
23	57.5%	(43.3%, 70.8%)
24	60.0%	(45.8%, 73.1%)

With a sample size of 40 study participants in Part-3B, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 33.1%, 55.4%, or 87.1%, respectively.

In Part-4, up to approximately 12 participants are expected to be enrolled. By assuming intra-subject variability of the steady-state AUC is[redacted], 12 participants will achieve a maximum imprecision of [redacted]. When 9 participants are PK evaluable, the maximum imprecision will be approximately [redacted].

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 20).

Table 20 - Populations for analyses

Population	Description
Enrolled	All participants who sign the ICF and have been allocated to an intervention regardless of whether the intervention was received or not.
DLT-evaluable (only for Part-1 and Part-3A)	Participants who take at least 4 of the 6 planned doses of SAR442720 and 28 of the 42 planned doses of adagrasib in the first cycle of the treatment and complete the DLT observation period. OR Participants who have any DLT observed in the DLT or DLT observation period.
PK	Participants who have at least one measurable SAR442720 concentration or at least one measurable pembrolizumab concentration or at least one measurable adagrasib concentration after the first dose
PDy	Participants who have at least one PDy marker result after the first dose
Safety	Participants who take at least one dose of any drug (ie, SAR442720, pembrolizumab or adagrasib)

Abbreviations: DLT = dose-limiting toxicity, ICF = informed consent form, PDy = pharmacodynamics(s), PK = pharmacokinetic(s).

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

All baselines are defined as the last assessment prior to the first dose unless specified otherwise. The MTD recommendation will be based on the DLT-evaluable population Cycle 1 data only. All safety and efficacy analyses will be based on the safety population unless otherwise specified. The Part-1 and Part-3A analyses will be performed separately by different dose levels unless specified otherwise. The Part-2 and Part-3B analyses will be presented separately, with Part-2 presented by different cohorts and overall, and Part-3B as a single cohort.

The analysis period will be divided into 3 segments:

- The pre-treatment period is defined as the time from when the participants give informed consent to the first administration of the IMP.
- The treatment period (ie, treatment-emergent period) is defined as the time from the first administration of IMP up to 30 days after the last administration of IMP.
- The post-treatment period is defined as the time from the 31 days after the last administration of IMP.

9.4.2 Efficacy endpoint(s)

Below table (Table 21) summarizes the efficacy endpoints involved in this study:

Table 21 - Summary of efficacy endpoints

Efficacy Endpoint	Part-1/3A	Part-2/3B	Part-4
ORR per RECIST v1.1	Secondary	Primary	Secondary
DoR	Secondary	Secondary	Secondary
PFS	NA	Secondary	NA
TTR	NA	Secondary	NA
CBR	NA	Secondary	NA
DCR	NA	Secondary	NA
OS	NA	Exploratory (only for Part-2)	NA
ORR per iRECIST	NA	Exploratory (only for Part-2)	NA

Abbreviations: CBR = Clinical benefit rate; DCR = disease control rate; DoR = duration of response, NA = not applicable; ORR = objective response rate, OS = overall survival; PFS = progression free survival, RECIST= Response Evaluation Criteria in Solid Tumors; TTR = time to response.

The ORR is defined as the proportion of participants who achieve a confirmed complete response (CR) or partial response (PR) per RECIST v1.1. Objective response rate and the corresponding 90% Clopper-Pearson 2-sided CI will be derived. Best overall response (BoR) per RECIST v1.1 will also be summarized. ORR per iRECIST will also be presented (for Part-2 only).

For Part-2 and Part-3B, the primary endpoint (ORR) analyses is performed when all participants have at least 2 post baseline tumor assessments with response durability demonstrated or discontinue study treatment (whichever occurs first).

Duration of response per RECIST v1.1 is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death due to any cause, whichever occurs first. Progression free survival per RECIST v1.1 is defined as the interval from the administration of the first IMP dose to the earlier of the first documentation of definitive disease progression or death due to any cause, whichever occurs first. Participants who are still alive and free from progression at the time of data cutoff date, are lost to follow-up, have discontinued from the study, or who have initiated subsequent anticancer therapy will be censored at the last adequate tumor assessment. The Kaplan-Meier estimates of the 25^{th}, 50^{th}, and 75^{th} percentiles and their associated 95% CI will be provided. The OS will also be summarized using Kaplan-Meier methods.

Time to response is defined as the interval from the administration of the first IMP dose to the first documented CR or PR which is confirmed by a subsequent response. The TTR will be summarized descriptively.

Clinical benefit rate is defined as the proportion of participants who achieved confirmed CR or PR at any time or SD for at least 6 months. The CBR and corresponding 90% Clopper Pearson 2-sided CI will be derived.

Disease control rate is defined as the proportion of participants who achieved confirmed CR or PR or SD. The DCR and corresponding 90% Clopper-Pearson 2-sided CI will be derived.

9.4.3 Safety endpoint(s)

Safety endpoints including incidence and severity of AEs and SAEs and laboratory abnormalities are the primary endpoints for Part-1 and Part-3A and secondary endpoint for Part-2, Part-3B, and Part-4.

9.4.3.1 Adverse events

The TEAE period is defined as the time from the first dose of study interventions up to 30 days after last dose of study interventions. Only TEAEs will be summarized in tables.

An overall summary of TEAEs will be provided. The number and percentage of participants who experience any of the following will be provided:

- TEAEs
- TEAEs of Grade ≥3
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment period)
- Serious TEAEs
- Serious treatment-related TEAEs
- TEAE leading to premature discontinuation of either SAR442720, pembrolizumab or adagrasib
- TEAE leading to definitive discontinuation
- TEAE leading to dose modifications
- Treatment-related TEAEs.
- Treatment-related TEAEs of Grade ≥3
- DLTs

The number and percentage of participants experiencing TEAEs by primary system organ class and PT will be summarized by NCI CTCAE version 5.0 grade (all grades and Grade ≥3). Similar tables will be prepared for treatment-related TEAEs, AESIs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, delay, omission, serious TEAEs and TEAEs with fatal outcome.

9.4.3.2 Clinical laboratory evaluations

Clinical laboratory test results will be graded according to NCI CTCAE Version 5.0, when applicable. Number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the TEAE period will be provided for the all-treated population.

When the NCI CTCAE Version 5.0 scale is not applicable, the number of participants with laboratory abnormality out-of-normal laboratory range value and potential clinically significant assessments will be displayed.

9.4.4 Other endpoint(s)

Concentrations of SAR442720, pembrolizumab, and adagrasib will be summarized with descriptive statistics.

For Part-3A and Part-4, PK parameter estimates, including but not limiting to the ones listed below, will be determined when possible for SAR442720 and adagrasib:

- C_{max} (observed)
- T_{max} (observed)
- AUC_{0-t} and AUC_{inf}, if possible
- $t_{1/2}$, if possible
- Accumulation ratio

Unless otherwise specified, the PK parameters will be estimated based on noncompartmental analysis methods. These estimates will be summarized descriptively by dose cohort. All PK parameters will be computed using the actual elapsed time calculated relative to dose administration.

For Part-4, the geometric mean ratios and 90% confidence intervals of AUC and C_{max} will be computed for SAR442720 between fed and fasted states of tablet formulation (C1D1 to C1D15) and between the tablet (test) and capsule (reference) formulations (C1D15 to C2D1). In addition, the PK parameters in Part-4 will be analyzed using a mixed effect model, which will be described in detail in the statistical analysis plan.

Population PK analysis may be conducted to obtain the PK parameters of SAR442720, pembrolizumab, and adagrasib. If performed, the results will be summarized in a separate report.

Exploratory analyses may be performed to evaluate the relationship between the estimated PK parameters and PDs, selected safety, biomarker, or clinical effect endpoints.

The PK and PDy analyses will be presented in a separate report.

All other safety endpoints (ie, vital signs, ECG, ECOG, etc) will be summarized.

9.5 INTERIM ANALYSES

There is no formal interim analysis planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH-GCP Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- 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 medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- 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) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 5 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples or new extra samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate consent will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate consent.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (General Data Protection Regulation).

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on afro American population for the United States Food and Drug Administration (FDA) or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- 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 to the Sponsor.
- 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 as described in the informed consent.
- 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.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data are intended to be used for the whole drug development program from collection to reimbursement.

10.1.5 Committees structure

The Study Committee will be comprised of the Principal Investigator from each site involved in the dose escalation phase, clinical team members from the Sponsor (including at least the Study Medical Manager and Global Study Manager, and experts, including the Global Safety Officer, pharmacokineticists, biostatisticians).

The Study Committee will review clinical data on a regular basis, with a review being performed at least at the end of each DL cohort, before the enrollment of new participants at the next DL, and at the end of the dose escalation phase of the study. The Study Committee in agreement with the Sponsor's Study Medical Manager will decide on whether to escalate or de-escalate to the next DL or to add alternative dose levels during Study Committee meetings based on current safety profile and tolerability, available PK information, and statistical design recommendation. Decisions regarding participant treatment and cohort expansion will be discussed and clearly documented in the discussion minutes. The Study Committee in agreement with the Sponsor's Study Medical Manager may permit the evaluation of additional DL and/or additional schedules of administration of SAR442720, depending upon the observed safety and DLT at each DL, and the safety and/or PK data observed in the ongoing Phase 1 monotherapy escalation study.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.7 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 (eg, 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.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of

noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report 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.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant first visit and will be the study start date.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. 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 study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10 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 before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- 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 studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 22 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.
- C2+Day 15 laboratory assessments could be done remotely if needed and after discussion with the Study Medical Manager.
- Pregnancy testing. Refer to Section 5.1 for screening criteria, Appendix 4 (Section 10.4) for WOCBP criteria and SoA (Section 1.3) for time points.

- Results of each test must be entered into the eCRF.

Table 22 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Bands (if available)
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils, other cells
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose nonfasting
	Potassium
	Sodium
	Chloride
	Bicarbonate
	Calcium
	Magnesium
	Phosphorous
	Uric acid
	Albumin
	Amylase
	Lipase
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Gamma-glutamyl transferase (GGT)
	Total and direct bilirubin
	Total protein
Routine urinalysis[b]	Specific gravity
	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
	Microscopic examination (if blood or protein is abnormal)
CPK isoenzymes	Total and heart muscle (MB) component (not required for screening purposes)

Laboratory assessments	Parameters
Other screening tests	Coagulation test to include prothrombin time (PT)/international normalized ration (INR) and aPTT (or partial thromboplastin time)
	Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)[c]
	Highly sensitive blood or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b]
	Serology: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis C virus antibody. If hepatitis C virus antibody is positive, then obtain hepatitis-C RNA
	The results of each test must be entered into the case report form (CRF).

NOTES :

a Concurrent elevation of AST or ALT >3 x ULN AND total bilirubin >2 x ULN or INR >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (possible Hy's law case). All events with the defined biochemical abnormalities must be reported as an SAE; and study medications should be permanently discontinued.

b Local urine testing will be standard for the protocol unless blood testing is required by local regulation or IRB/IEC. For screening a blood test is required.

c See Appendix 4 (Section 10.4).

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

- 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 intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a) Results in death

b) 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 were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

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.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person'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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- 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.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, 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 the Sponsor in lieu of completion of the AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

Adverse events will be graded according to the NCI CTCAE Version 5.0. NOTE: The seriousness and intensity of an event are assessed independently of each other. An event is defined as "serious" when it meets at least 1 of the predefined criteria as described in the above definition of an SAE, and can be assessed as any grade. A nonserious event may be assessed as either CTCAE Grade 1 or 2. Although CTCAE Grade 3 nonserious events are possible in some circumstances, the Investigator should carefully consider whether the event is best classified as serious. Any AE which is either a CTC Grade 4 (life threatening) or Grade 5 (has death as an outcome) is by definition an SAE.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours of first learning of the SAE.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor by telephone.

SAE reporting to the Sponsor via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A male participant must agree to use contraception during the intervention period and for at least 6 months after the last dose of study intervention.

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

- Not a WOCBP OR
- A WOCBP as defined below who agrees to follow the contraceptive guidance during the intervention period and for at least 6 months after the last dose of study intervention as described below.

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

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

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE:

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial 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 and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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 intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 APPENDIX 5: GENETICS

Use/Analysis of Tumor DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood and tumor tissue samples will be collected for DNA analysis from consenting participants.
- DNA samples from tumor tissue will be retrospectively analyzed to explore clinical activity in participants with specific molecular abnormalities. In addition, predefined biomarkers for the sensitivity to SHP2 and/or MEK1/2 inhibition will be evaluated.
- DNA extracted from archival participant tumor tissue will be used to evaluate if a participant has specific tissue abnormalities in their DNA that may be sensitive to SAR442720, adagrasib, and pembrolizumab. This information will be used to confirm if a participant has the same mutations as their local genetic results (noncentralized testing laboratory) report. The local report is the basis for eligibility assessment.
- Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- DNA and RNA from fresh tumor tissue will be used for research related to study intervention or NSCLC and/or other solid tumors. Genetic research will include whole exome and transcriptome studies, which will be conducted on tissue (where sufficient tissue is available) to explore if DNA and RNA can help identify potential biomarkers associated with response to SAR442720, adagrasib, and pembrolizumab. In addition, the biomarker of sensitivity in blood, namely ctDNA and peripheral blood mononuclear cell (PBMC) transcriptome will be explored.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will remove all participant identifiers from the participant samples to inhibit recognition or reidentification. The anonymized DNA samples will be stored in a secure storage space prior to testing for markers of drug sensitivity. All samples will be processed and analyzed for the purposes of this study and the output will be anonymized participant data, which may be applied for future research.

- Participant sample retention will not exceed 15 years or as per local requirements following the last participant's last visit for the study.

Use/Analysis of normal PBMC DNA

- Where local regulations and IRB/IEC allow, blood samples will be collected for DNA analysis from consenting participants in Part-2. PBMC DNA will be analyzed with tumor DNA to study tumor specific mutations.

10.6 APPENDIX 6: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.7 APPENDIX 7: RESPONSE EVALUATION CRITIERIA IN SOLID TUMORS (RECIST V1.1)

For this study, response and progression will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors guideline version 1.1 (RECIST v1.1; Eisenhauer 2009).

Measurability of Tumor at Baseline

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows.

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 examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 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 no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

Nonmeasurable Tumor Lesions
All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), and as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion,

inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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 measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic 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.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

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.

METHODS 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 follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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 and MRI

CT is the best currently available and reproducible method to measure lesions selected for response assessment. 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 in certain situations (eg, for body scans).

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy and Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a participant to be considered in complete response.

Cytology and Histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (eg, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

BASELINE DOCUMENTATION OF "TARGET" AND "NONTARGET" LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 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 that if a participant has only one or 2 organ sites involved, a maximum of 2 and 4 lesions, respectively, will be recorded.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those that lend themselves to reproducible 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

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, 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 × 30 mm has a short axis of 20 mm and qualifies as a malignant measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 but <15 mm) should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

Sum of Diameters

A sum of the diameters (longest for non-nodal lesions and short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. As noted above, if lymph nodes are to be included in the sum, 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 nontarget 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." In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm).
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). 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.

Special Notes on Assessment of Target Lesions

Lymph Nodes:

Lymph nodes identified as target lesions should always have the short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm. Thus, when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate Section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, stable disease (SD), and progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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 (eg, 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as "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 (derived from 5-mm slice thickness).

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. To reiterate, however, if the radiologist is able to provide an actual measurement, it should be recorded even if it is below 5 mm.

Lesions that Split or Coalesce on Treatment:

When non-nodal lesion "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".

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although 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.

Response	Evaluation of Nontarget Lesions
Complete Response (CR)	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis)
Non-CR/ Non-PD	Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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 nontarget disease such 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 quality 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 Nonmeasurable 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 nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable), 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 nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in "volume," which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal (ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor [eg, some "new" bone lesions that may be simply healing or flare of pre-existing lesions]). This is particularly important when the participant's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the participant who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, eg, 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.

FDG-PET

While fluorodeoxyglucose PET (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion
  - A positive FDG-PET scan lesion is one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan)
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
    A "positive" FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image

EVALUATION OF BEST OVERALL RESPONSE

The BoR is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The participant's BoR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Time point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 23 provides a summary of the overall response status calculation at each time point for participants who have measurable disease at baseline.

When participants have nonmeasurable (therefore non-target) disease only, Table 24 is to be used.

Table 23 - Time point response: Participants with target lesions (with or without nontarget lesions)

Target Lesions	Nontarget Lesions	New Lesion	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

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Table 24 - Time point response: Participants with nontarget lesions only

Nontarget 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

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease.

a Non-CR/non-PD" is preferred over "stable disease" for nontarget disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Unevaluable Designation

When no imaging/measurement is done at all at a particular time point, the participant is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE 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 the 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.

Best Overall Response: All Time points

The BoR is determined once all data for the participant is known.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the BoR can be interpreted as in Table 25.

Table 25 - Best overall response when confirmation is required

Overall Response at First Time point	Overall Response at Subsequent Time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

a If a CR is truly met at the first time point, any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the 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 participant 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.

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.

In trials where confirmation of response is required, repeated “NE” time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a participant with time point responses of PR-NE-PR as a confirmed response.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such participants is to be determined by evaluation of target and nontarget disease as shown in Table 23, Table 24, and Table 25.

Conditions that define "early progression, early death and un-evaluability" are study-specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine-needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

10.8 APPENDIX 8: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

ECOG Performance Status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

10.9 APPENDIX 9: GENERAL GUIDELINES FOR THE MANAGEMENT OF ADVERSE EVENTS

Investigators must be extremely vigilant and be ready to intervene early in the management of AEs, particularly immune-related AEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle.

- Detailed guidance for the management of specific AEs (colitis, endocrine AE, pneumonitis, renal AE, dermatologic AE, hepatitis, ophthalmologic AE [uveitis], etc.) is provided in Table 27.
- General guidance is provided in Table 26 below.
- If a participant experiences several AEs which involve different recommendations, the most conservative recommendation should be followed.

The recommendations provided in Table 26 and Table 27 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual participant.

Table 26 - General guidelines

Severity	Withhold/restart /discontinue SAR442720 treatment	Withhold/restart/discontinue the combination drug (Pembrolizumab or adagrasib) treatment	Supportive care
Grade 1	No action	No action	Provide symptomatic treatment.
Grade 2	No action	May delay or omit the pembrolizumab dose until Grade ≤1 Adagrasib dose modification/ dose interruption per Investigators discretion unless otherwise defined in Table 27.	Consider systemic corticosteroids (Prednisone 0.5 to 1 mg/kg/day or equivalent) in addition to appropriate symptomatic treatment.
Grade 3	Delay the treatment until toxicity improves to Grade ≤1 or baseline.		For any Grade 3-4 immune-related adverse event, if symptoms worsen or do not improve on adequate corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) within 48 to 72 hours), consider additional immunosuppressive agents (to be selected from agents such as: infliximab, cyclophosphamide, cyclosporine and mycophenolate mofetil). Referral of the participant to a specialized unit for assessment and treatment should be considered.
Grade 4	Permanently discontinue		

Table 27 - Dose modification guidelines for combination regimens (SAR442720 and pembrolizumab combination or SAR442720 and adagrasib combination)

AE	Action
Skin reactions	Grade 1 or 2 (tolerable): Administer supportive care and continue study drugs Intolerable Grade 2-Grade 3: Hold both drugs until < Grade 2. If improves to < Grade 2 within 4 weeks, then reduce SAR442720 by one dose level and resume combination drugs at the same dose level. Suspected Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN): Withhold both drugs until adverse reactions recover to Grade 0-1. Grade 4: Hold both drugs until < Grade 1. If improves to < Grade 1 within 4 weeks, resume, reduce SAR442720 by two dose levels and resume combination drugs at the same dose level. Grade 4 or confirmed SJS or TEN: Permanently discontinue both drugs If ≥ Grade 3 rash recurs despite two SAR442720 dose level reductions, permanently discontinue both drugs. If rash does not improve within 4 weeks, permanently discontinue both drugs.
Ocular symptoms > Grade 2	Hold both study drugs and obtain ophthalmology consult. RVO: Any grade, permanently discontinue both drugs (Part-1, 2, and 4 only). In Part-3 permanently discontinue SAR442720 but may continue adagrasib, please consult with the Medical Monitor. Neurosensory retinal detachment: Hold both drugs until resolution to ≤ Grade 1. If resolves within 4 weeks, then reduce SAR442720 by one dose level. If visual symptoms > Grade 2 recur despite two dose level reductions, permanently discontinue both drugs. (Part-1, 2 and 4 only). In Part-3 permanently discontinue SAR442720 but may continue adagrasib, please consult with the Medical Monitor. Uveitis/iritis > Grade 2: Hold both study drugs. If resolves to ≤ Grade 1 within 4 weeks, then reduce SAR442720 dose by one level and resume both study drugs. If recurs despite two dose level reductions of SAR442720, permanently discontinue both drugs. If > Grade 1 symptoms recur or follow-up ophthalmology examination results worsen, withhold treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib) and either further decrease dose or permanently discontinue treatment. Other > Grade 2 AE: Hold SAR442720. If AE doesn't improve within 2 weeks, then consider holding the combination drug. If no improvement within 4 weeks from onset, consider permanently discontinuing both drugs. In ambiguous cases, please consult with the Medical Monitor.
Hemorrhage > Grade 3	Rule out other causes. Grade 3: Hold both study drugs until resolution to ≤ Grade 1. If hemorrhage is associated with thrombocytopenia or reduced platelet count from baseline hold both drugs. In Part-1, 2, and 4, if resolves within 4 weeks, consider restarting SAR442720 at a lower dose and restarting pembrolizumab at same dose (dose reduction is not allowed for pembrolizumab). In Part-3, if resolves within 4 weeks, consider restarting SAR442720 and adagrasib at a lower dose. In ambiguous cases, please consult with the Medical Monitor. Grade 4 or CNS hemorrhage: permanently discontinue both drugs.
Diarrhea and other GI toxicities	Grade 1-2 Diarrhea: Maximal supportive care. Continue both drugs at current doses. Grade ≥3 Diarrhea: Hold both study drugs (if receiving maximal supportive care) until ≤Grade 1. If improves within 4 weeks, then dose reduce SAR442720 and adagrasib (in Part-3), and start pembrolizumab at same dose (in Part1, 2 and 4); if diarrhea is not resolved to ≤ Grade 1 within 4 weeks, permanently discontinue both drugs. Grade 3 Nausea >72 hours despite therapy; hold both drugs until ≤ Grade 1 or return to baseline, dose reduce SAR442720 and adagrasib (in Part-3), Grade ≥3 Pancreatitis, permanently discontinue both drugs. Asymptomatic Grade 3 Amylase or Lipase Elevation >8 days, hold until ≤ Grade 1 or return to baseline, resume both drugs at same dose.

AE	Action
Colitis	Grade 2 or 3: Withhold both study drugs until adverse reactions recover to Grades 0 to 1. Grade 4 or recurrent Grade 3: Permanently discontinue both study drugs. Please consult Medical Monitor for ambiguous cases.
Hepatitis, liver function test abnormalities (AST, ALT, and/or total bilirubin)	Grade 1: Continue both study drugs at current doses. Grade 2: In Part-1, 2, and 4, continue SAR442720 and withhold pembrolizumab until adverse reactions recover to Grade 0 to 1 In Part-3, continue SAR442720 and reduce adagrasib one dose level. Grade 3: Rule out other causes such as metastatic liver disease, concomitant drugs, infection, etc. Withhold both study drugs until improves < Grade 1, then dose reduce SAR442720 and adagrasib one dose level (in Part-3) and resume pembrolizumab at the same dose (Part-1, 2 and 4). If AE does not improve or recurs, dose reduce another dose level of SAR442720. No dose modification required for isolated GGT. In Part-1, 2, and 4 hold SAR442720; if no improvement in LFTs after SAR442720, withhold pembrolizumab as well. If Grade ≥3 with AST or ALT occurs, permanently discontinue both study drugs. In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥50% and lasts ≥1 week: Permanently discontinue pembrolizumab. Action with SAR442720 or adagrasib should be discussed with the Medical Monitor. Grade 4: see general Grade 4 non-heme AEs. In Part-1, 2, and 4 hold both SAR442720 and pembrolizumab. If resolves, restart both medications, SAR442720 at reduced dose (pembrolizumab dose reduction is not allowed). If no improvement to < Grade 1 within 4 weeks, permanently discontinue both drugs. In Part-3 permanently discontinue both study drugs. Concurrent treatment-emergent / treatment related elevation of AST or ALT >3 x ULN AND total bilirubin >2 x ULN or INR >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (possible Hy's law case). Both medications should be permanently discontinued. If liver injury is due to other causes such as viral hepatitis, acute liver disease, or another drug capable of liver injury, evaluate the extent of liver injury (eg, albumin level, PTT, INR etc) and if considered to be severe, discontinue both medications.
QTcF prolongation	Rule out other factors for arrhythmia including myocardial ischemia, electrolyte abnormalities, and concomitant medications. Evaluate concomitant medications that prolong QTcF (eg, 5-HT3 receptor antagonist anti-emetics etc) and discontinue the suspected concomitant medication, as feasible. Hold discontinue both study drugs per below instructions. Consult cardiology. Grade ≥3: Hold both study drugs until QTcF <480 msec; correct electrolytes; consult cardiology. If resolves within 4 weeks, restart both drugs; SAR442720 and adagrasib at one dose level lower (pembrolizumab dose reduction is not allowed); otherwise permanently discontinue. Repeat ECG at 2 weeks and 4 weeks after restarting. Perform additional ECGs monitoring at D15 of each subsequent cycle for 3 cycles then as instructed by the SoA. For recurrence of QTc prolongation follow the guidelines above and reduce dose of SAR442720 and adagrasib by another dose level (pembrolizumab dose reduction is not allowed). Permanently discontinue both SAR442720 and pembrolizumab if after correction of associated risk factors and dose reductions, the QTcF increase meets values of both >500 msec and >60 msec change from pre-treatment values. In Part-3: If QTcF Prolongation* > 500 msec and increases by > 60 msec on at least 2 ECGs ≤ 22 days, hold adagrasib until ≤ Grade 1 or return to baseline (<15 msec above baseline). Resume adagrasib at one or two dose levels lower. If QTcF Prolongation* > 500 msec and increases by > 60 msec on at least 2 ECGs > 22 days, discontinue adagrasib.

AE	Action
Reduction in LVEF and other cardiac toxicities	Asymptomatic reduction: absolute decrease in LVEF ≥ 20% from baseline and below LLN, withhold treatment (either SAR442720 and pembrolizumab or SAR442720 and adagrasib) for up to 4 weeks and repeat echocardiogram (ECHO) for LVEF at 2, 4, 10, and 16 weeks after hold. Restart at reduced dose if LVEF ≥ LLN and absolute decrease from baseline LVEF < 20%. Permanently discontinue if symptoms of heart failure are present. Symptomatic reduction: In case of symptomatic systolic dysfunction with an LVEF decrease from baseline ≥10% and/or below LLN, withhold both SAR442720 and pembrolizumab for up to 4 weeks and consider permanent discontinuation if considered causative; in Part-3 permanently discontinue SAR442720 and adagrasib. Consult cardiology and the Medical Monitor. If reinitiating treatment, ALL of the following must be present: an EF decrease not considered to be associated with the study drug, symptoms resolve, LVEF > LLN, and absolute decline from baseline was <10%; otherwise, permanently discontinue both drugs. If reinitiating treatment, restart both study drugs, SAR442720 and adagrasib at a lower dose (pembrolizumab dose reduction is not allowed). Please consult with the Medical Monitor for individual cases. All participants who require dose reduction of SAR442720 due to treatment related systolic dysfunction should have ECHO at 2 weeks, 4 weeks, 10 and 16 weeks, then per protocol or as clinically indicated. In Part-3: For all other Grade ≥3 cardiac toxicities/adverse drug reactions hold study treatment until recovery to ≤ Grade 1 or to baseline. Adagrasib/SAR442720 treatment may resume at one dose level lower. For QTc prolongation please refer to the previous bullet. Please consult with the Medical Monitor for individual cases.
Hypertension	Grade 2: Treat according to institutional guidelines with goals blood pressure < Grade 1. Continue both drugs. Grade 3: Treat according to institutional guidelines with goal blood pressure < Grade 1. Consider holding SAR442720 and continue pembrolizumab and adagrasib. If improved restart SAR442720 at reduced dose level. Grade 4: Treat according to institutional guidelines. Discontinue both SAR442720 and pembrolizumab. In Part-3 hold adagrasib until ≤Grade 1 or baseline, then may resume one dose level lower.
Hematologic lab abnormalities > Grade 3	Assess for other causes. Hold concomitant medications associated with myelosuppression. Grade 3 neutropenia, thrombocytopenia: Hold both drugs if clinically indicated until < Grade 1 or baseline. If improves within 4 weeks, restart pembrolizumab or adagrasib at same dose and administer SAR442720 one dose level lower. If does not improve within 4 weeks, discontinue both drugs. Grade 3 febrile neutropenia: Hold both drugs until fever resolves and ANC < Grade 1 or baseline. If improves within 2 weeks, restart pembrolizumab at same dose and SAR442720 and adagrasib 1 dose level lower. If does not improve within 2 weeks, discontinue both drugs. Grade 3 anemia: Assess transfusion history. Transfuse per institutional guidelines. Continue pembrolizumab, and hold SAR442720 if clinically indicated until < Grade 1. If improves within 4 weeks, restart SAR442720 one dose level lower. If does not improve within 4 weeks, consider discontinuation of both drugs. Hold adagrasib until ≤ Grade 1 or baseline and may resume at the same dose level. Grade 4 cytopenias: Hold both drugs until resolves to < Grade 1 or baseline. If improves within 4 weeks, restart both drugs; reduce both SAR442720 and adagrasib one dose level lower (pembrolizumab dose reduction is not allowed). If does not improve within 4 weeks, discontinue both drugs. Thrombocytopenia associated with clinically significant bleeding, at any level: Hold both drugs and follow hemorrhage recommendations. Uncomplicated Thrombocytopenia (without clinically significant bleeding): Grade 1 to 2: Continue treatment at current dose level and frequency and monitor closely Grade 3 to 4: Manage per institution guidelines and interrupt dosing of both study drugs until participant recovers to Grade 1 or better. If recovery occurs, the investigator may resume dosing both study drugs at the same dose level and frequency, if clinically appropriate. If Grade 3 to 4 events recur again, hold dose until recovery to Grade 1 or better and consider re-introducing study drug at reduced frequency, or withdrawing participant from study therapy. Please contact Medical Monitor for ambiguous cases.

AE	Action
Other non-hematologic AEs	Intolerable Grade 2 or Grade 3: Hold both drugs until ≤ Grade 1. If improves within 4 weeks, then resume pembrolizumab at same dose and dose reduce SAR442720 in Part-1, 2, 4. In Part-3 dose reduce both SAR442720 and adagrasib; if not resolved.to ≤Grade 1 within 4 weeks, permanently discontinue both drugs (SAR442720 and pembrolizumab or SAR442720 and adagrasib). If event recurs, hold both drugs and consider dose reduction the drug not previously dose reduced upon improvement ≤ Grade 1. Grade 4: Consider permanent discontinuation both drugs. Otherwise, discuss with sponsor Medical Monitor and hold both drugs until ≤ Grade 1, if improves within 4 weeks, then consider resuming pembrolizumab, and both SAR442720 and adagrasib with dose reduction (pembrolizumab dose reduction is not allowed). Of SAR442720. For recurrent Grade 4 AE, permanently discontinue both drugs. Based on the investigator's assessment of the AE, either one, both SAR442720 and pembrolizumab or SAR442720 and adagrasib may be held if a clear attribution may be established. Grade ≥3 non hematological laboratory abnormalities if clear attribution may be established hold both drugs, upon improvement to ≤ Grade 1 resume SAR442720 and adagrasib lower dose level; resume pembrolizumab same dose level. Grade ≥3 non hematological laboratory abnormalities if clear attribution may be established hold both drugs, upon improvement to ≤ Grade 1 resume SAR442720 and adagrasib lower dose level; resume pembrolizumab at same dose level.
Nephritis	Grade 2 with creatinine >1.5 to ≤3 times upper limit of normal (ULN): In Part-1, 2, and 4 continue SAR442720 and withhold pembrolizumab until adverse reactions recover to Grade 0 to 1. In Part-3, continue SAR442720 and consider continuing adagrasib at the same dose level or one dose level lower. Grade ≥3 with creatinine >3 times ULN: Permanently discontinue pembrolizumab. In Part-3, if Grade ≥3 creatinine increased ≤22 days hold adagrasib until ≤ Grade 1or return to baseline, then adagrasib treatment may resume at the same dose level or one dose level lower. For Grade ≥3 creatinine increased >22 days discontinue adagrasib. Action taken with SAR442720 should be discussed with Medical Monitor depending on the clinical case.
Endocrinopathies (applies to Part-1, 2, 4)	Grade 2 adrenal insufficiency and hypophysitis: continue SAR442720 and withhold pembrolizumab until controlled by hormone replacement. Grade 3 or 4 adrenal insufficiency or symptomatic hypophysitis, Type 1 diabetes associated with Grade ≥3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis. Hyperthyroidism Grade ≥3: continue SAR442720 and withhold pembrolizumab until adverse reactions recover to Grades 0 to 1. For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise pembrolizumab treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Other immune-related adverse reactions (applies to Part-1, 2, 4)	Based on the severity and type of reaction (Grade 2 or Grade 3): Continue SAR442720 and withhold pembrolizumab until adverse reactions recover to Grades 0 to 1. SAR442720 may need to be withheld temporarily depending on the individual case assessment. Grade 3 or Grade 4 myocarditis; Grades 3 or Grade 4 encephalitis; Grade 3 or Grade 4 Guillain-Barre syndrome and all Grade 4 or recurrent Grade 3 immune related adverse reactions: Permanently discontinue both study drugs. Consult with Medical Monitor as necessary.
Pembrolizumab Infusion-related reactions (applies to Part-1, 2, 4)	Grades 3 or Grade 4 infusion related reactions: Permanently discontinue pembrolizumab.

AE	Action
Pneumonitis	Part-1, 2, and 4: For Grade 2 hold both drugs and re-start when toxicity resolves to ≤Grade 1 For Grades 3 and 4 – Permanently discontinue treatment with pembrolizumab and withhold SAR442720. However, once recovered to ≤Grade 1, treatment with SAR442720 may be re-started at a lower dose. In Part-3; Grade 1 consider reducing adagrasib by one dose level. Grade 2 hold adagrasib until ≤ Grade 1 or return to baseline. If resumed, decrease by one dose level lower. For Grade 2 recurrent or Grade 3 pneumonitis, discontinue both study drugs.

"Both study drugs" refer to either SAR442720 and pembrolizumab (in Part-1, 2, and 4) or SAR442720 and adagrasib (in Part-3)

10.10 APPENDIX 10: MEDICATION CLASSES THAT POTENTIALLY PROLONG QTC, STRONG CYP3A INHIBITORS AND/OR INDUCERS, PROTON PUMP INHIBITORS, H-2 RECEPTOR ANTAGONISTS, STRONG P-GP INHIBITORS AND OTHER PROHIBITED MEDICATION CLASSES

A partial list of drug classes that potentially prolong QTc, drugs that are strong CYP3A inhibitors and/or inducers, drugs that are proton pump inhibitors and H-2 receptor antagonists, drugs that are strong P-gp inhibitors, and other prohibited medications classes is provided below.

Medications known to prolong QTc		
Amiodarone	Anagrelide	Arsenic Trioxide
Azithromycin	Chloroquine	Chlorpromazine
Cilostazol	Ciprofloxacin	Citalopram
Disopyramide	Dofetilide	Donepezil
Dronedarone	Droperidol	Erythromycin
Escitalopram	Flecainide	Fluconazole
Haloperidol	Ibutilide	Levofloxacin
Methadone	Moxifloxacin	Ondansetron
Oxaliplatin	Pentamidine	Pimozide
Procainamide	Propofol	Quinidine
Sevoflurane	Sotalol	Terfenadine
Thioridazine	Vandetanib	Gatifloxacin
Clarithromycin	Cocaine	Domperidone
Donepezil	Hydroxychloroquine	
Strong CYP3A Inhibitors		
Boceprevir	Idelalisib	Posaconazole
Clarithromycin	Indinavir and ritonavir	Ritonavir
Cobicistat	Itraconazole	Saquinavir and ritonavir
Conivaptan	Ketoconazole	Telaprevir
Danoprevir and ritonavir	Lopinavir and ritonavir	Tipranavir and ritonavir
Diltiazem	Nefazodone	Troleandomycin
Elvitegravir and ritonavir	Nelfinavir	Voriconazole
Grapefruit juice	Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	

Atazanavir	Telithromycin	
Strong CYP3A Inducers		
Carbamazepine	Mitotane	Rifampin
Enzalutamide	Phenytoin	St. John's wort
Apalutamide	Phenobarbital	
Proton Pump Inhibitors (PPIs)		
Omeprazole	Lansoprazole	Dexlansoprazole
Rabeprazole	Pantoprazole	Esomeprazole
Ilaprazole		
H-2 Receptor Antagonists		
Ranitidine	Famotidine	Cimetidine
Nizatidine		
Strong P-gp Inhibitors		
Amiodarone	Carvedilol	Clarithromycin
Dronedarone	Itraconazole	Lapatinib
Lopinavir and Ritonavir	Propafenone	Quinidine
Ranolazine	Ritonavir	Saquinavir and Ritonavir
Telaprevir	Tipranavir and Ritonavir	Verapamil
CYP3A Substrates with Narrow Therapeutic Index		
Alfuzosin	Alprazolam	Budesonide
Conivaptan	Cyclosporine	Dihydroergotamine
Eletriptan	Eplerenone	Ergotamine
Everolimus	Fentanyl	Lomitapide
Lovastatin	Lurasidone	Midazolam
Naloxegol	Nisoldipine	Ranolazine
Rivaroxaban	Sildenafil	Simvastatin
Sirolimus	Ticagrelor	Tolvaptan
Triazolam		
Strong Inhibitor of BCRP		
Eltrombopag	Curcumin	Cyclosporine
CYP2B6 Substrates with Narrow Therapeutic Index		
Bupropion	Cyclophosphamide	Efavirenz
CYP2C9 Substrates with Narrow Therapeutic Index		
Warfarin		
CYP2C9 Moderate/Sensitive Substrates		
Celecoxib	Glimperide	Tolbutamide
CYP2D6 Substrates with Narrow Therapeutic Index		
Thioridazine	Pimozide	
CYP3A Moderate/Sensitive Substrates		
Alfentanil	Aprepitant	Atorvastatin

Avanafil	Buspirone	Colchicine
Darifenacin	Ebastine	Eliglustat
Felodipine	Ibrutinib	Maraviroc
Quetiapine	Rilpivirine	Sildenafil
Tacrolimus	Tadalafil	Vardenafil
P-gp Substrates with Narrow Therapeutic Index		
Dabigatran	Digoxin	
Antacids and H2-antagonists		
Cimetidine	Famotidine	Nizatidine
Ranitidine		

Please note that this list is not comprehensive.

The list and updates of medications that are known to prolong QTc may be obtained from www.crediblemeds.org.

For additional information and updates concerning strong CYP3A inhibitors and inducers and strong P-gp inhibitors, refer to the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

In addition, consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. Contact the Medical Monitor if questions arise regarding medications not listed.

10.11 APPENDIX 11: SIMULATION REPORT – ASSESSMENT OF PERFORMANCE

In Part-1 and Part-3A, there are not many dose levels included in the dose escalation. Therefore, interval design, specifically mTPI2, will be used in the dose escalation process.

The goal of assessing the mTPI2 design's performance is to evaluate its overall operating characteristics by comparing with 3+3 design under a range of scenarios for hypothetical DLT dose-response relationship that may occur during the conduct of the study. Here, the performance comparison of mTPI2 and 3+3 is presented for Part-1. Since the mTPI2 and 3+3 designs both consider doses in a discrete space, the performance comparison will be considered similar for Part-1 and Par-3A.

SPECIFICATION OF SIMULATION SCENARIOS

The planned starting dose levels are 100 mg (Dose level 1), 140 mg (Dose level 2) and 200 mg (Dose level 3). The first cohort will start with 140 mg.

Four scenarios were defined for DLT rate at all dose levels as shown in Figure 6. The scenarios were selected to represent a wide range of possible cases: the true MTD is dose level 2 (Scenario 2 and 3), dose level 3 (Scenario 1) and even higher than dose level 3 (Scenario 4).

Please note that it is strongly believed that the chance of dose level 1 being the MTD is extremely low based on the monotherapy results. Therefore, the scenario of dose level 1 being the MTD is not in the consideration. Also, the Scenario 2 and 3 have the same DLT trend. They cover the lower and upper bounds of the target toxicity interval at dose level 2. In order to make the plot self-explained, indicators will be used along with each scenario. For each dose level, “L” indicates low rate of DLT, and “T” indicates target rate of DLT which refers to MTD. “H” indicates high rate of DLT. For example, Scenario 1 would be indicated as LLT while Scenario 4 would be indicated as LLL.

PERFORMANCE

To evaluate the design performance for the 4 scenarios described above, the following measures will be discussed.

- Probability of a dose level selected as MTD
- Mean number of participants treated at each dose level

Results based on n=1000 simulated trials. The target DLT rate is set to be [redacted].

Abbreviations: DLT = dose-limiting toxicity, H = high rate of DLT, L = low rate of DLT, T = target rate of DLT which refers to MTD

Using the hypothetical scenarios specified above, the results for mTPI2 are plotted in Figure 7 and Figure 9. The results from 3+3 design are presented in Figure 8 and Figure 10 for a comparison purpose.

In general, mTPI2 design can find the true MTD more accurately than the 3+3 design. The 3+3 design is more conservative than the mTPI2. The chance of finding the correct MTD (in red) is higher than any other dose level for all scenarios in mTPI2 design. While in Scenario 2 and 3, 3+3 design is much conservative to recommend the 100 mg as MTD in more than [redacted] of simulated trials. Specifically, when the true DLT rate changes from [redacted] in Scenario 2 to [redacted] in Scenario 3, the 3+3 design will recommend 100 mg from [redacted]. The mTPI2 recommends the 140 mg as MTD consistently ([redacted]) in both scenarios. In Scenario 1, the 3+3 design is not able to differentiate 140 mg and 200 mg when the true MTD is 200 mg ([redacted]). Even in Scenario 4 where the true MTD is >200 mg, the 3+3 design still identify the MTD as <100 in [redacted] of the simulations. Also, when 2 DLTs were observed out of 3 participants, the 3+3 design will claim the MTD has to be lower than the current dose level while the mTPI2 design will just recommend a lower dose level for the next cohort but keep the decision of recommending the current dose level open. Overall, the accuracy of mTPI2 is satisfactory and 3+3 is too conservative.

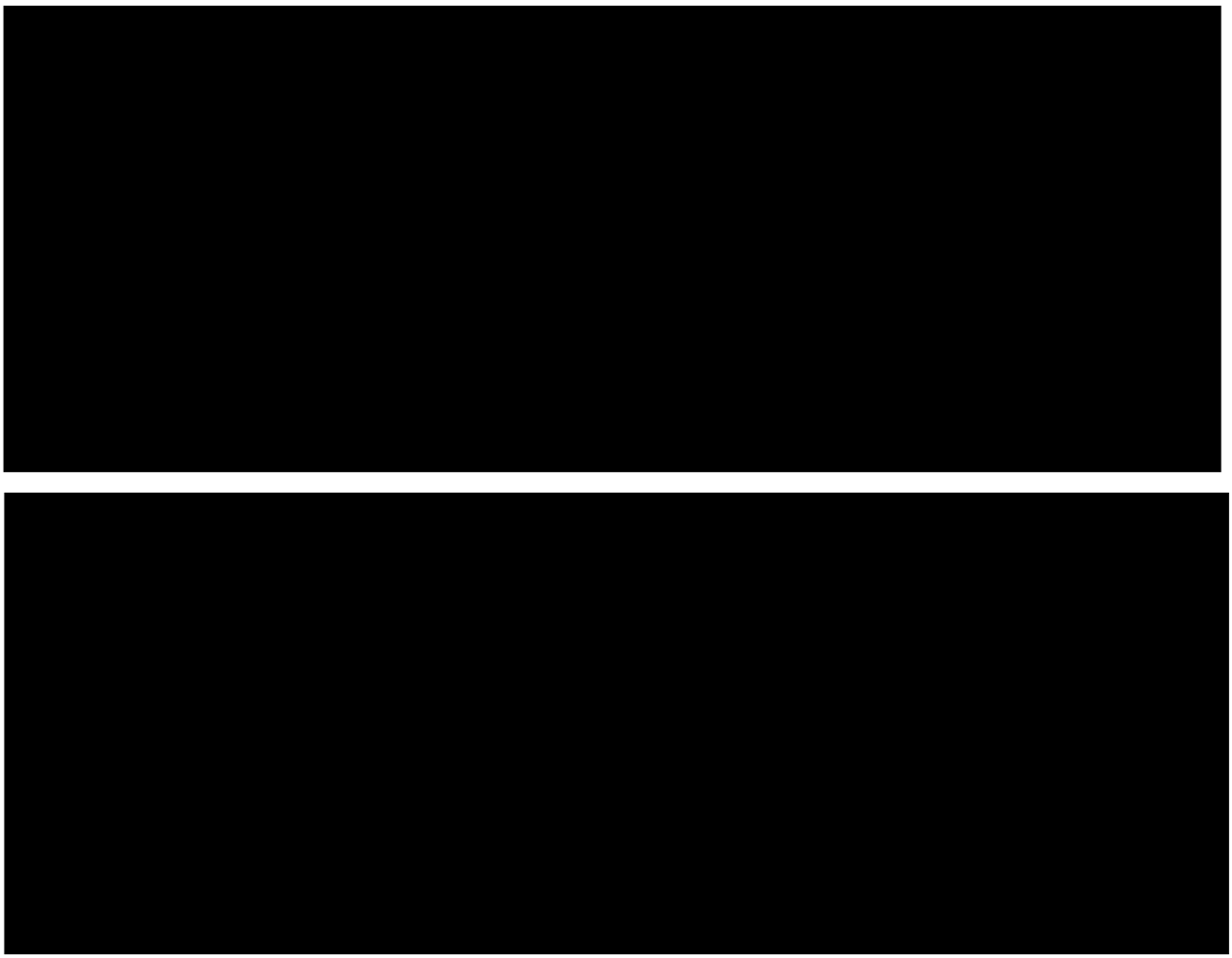
The sample size needed for both designs are roughly 3 cohorts (9 participants) for all scenarios. But more participants are treated at a dose level below the MTD in 3+3 compared to mTPI2 ([redacted]) because 3+3 is too conservative.

To conclude, mTPI2 design can provide a more accurate MTD recommendation compared to 3+3 design with similar sample size.

Figure 7 - Probability of a dose level selected as MTD for mTPI2

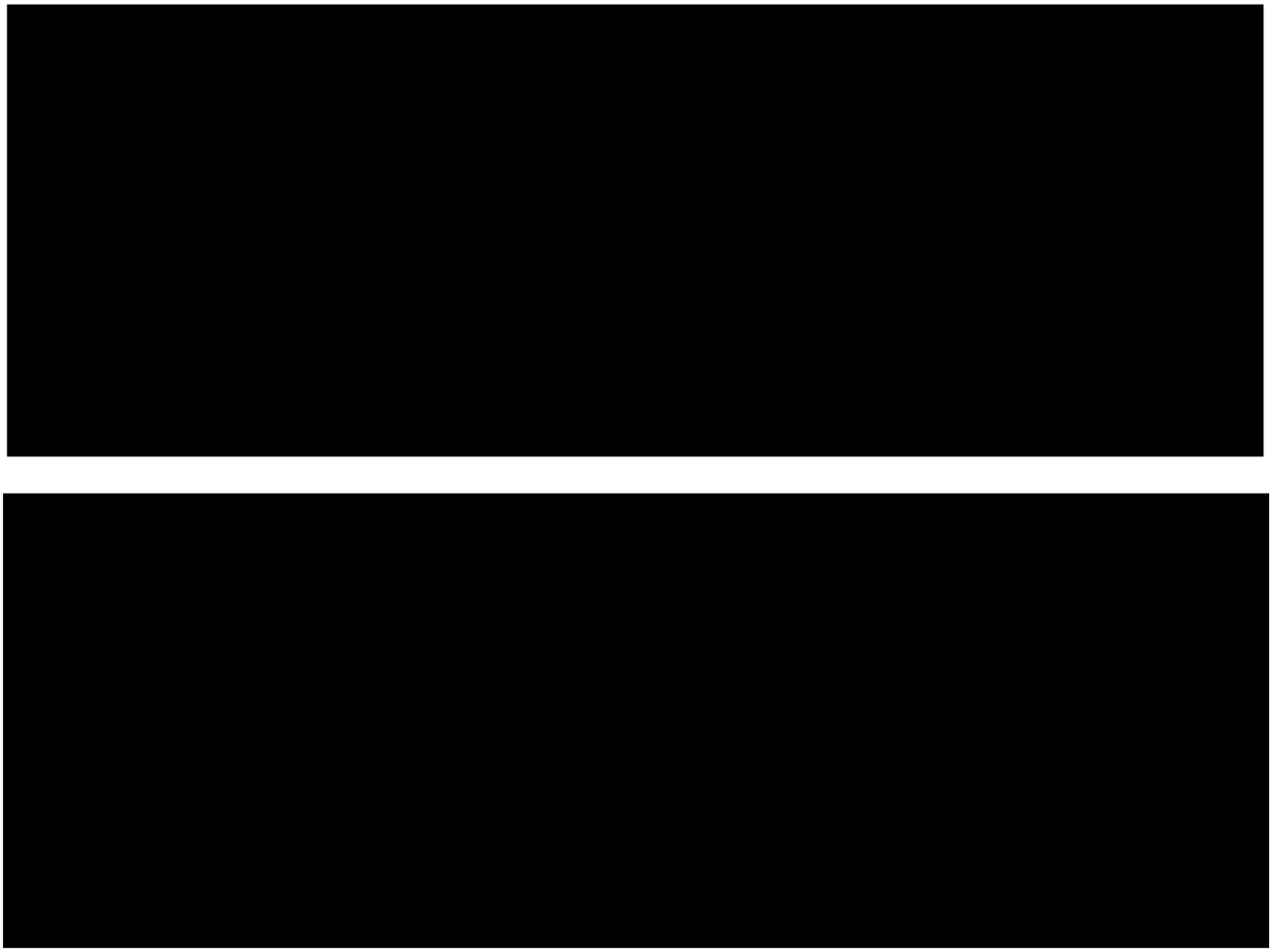
Abbreviations: H = high rate of DLT, L = low rate of DLT, MTD = maximum tolerated dose, mTPI2 = modified toxicity probability interval 2, T = target rate of DLT which refers to MTD

Figure 8 - Probability of a dose level selected as MTD for 3+3



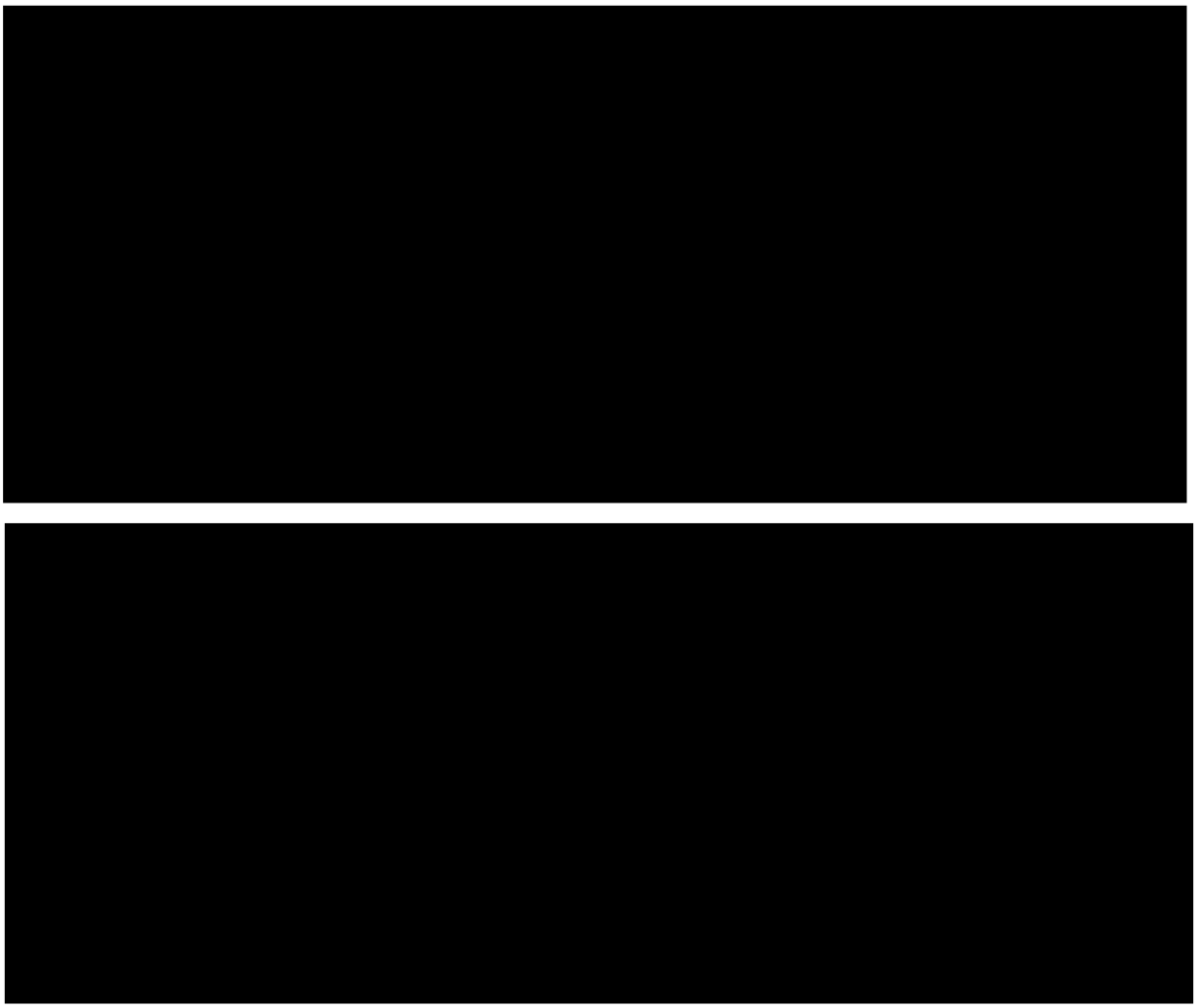
Abbreviations: H = high rate of DLT, L = low rate of DLT, MTD = maximum tolerated dose, T = target rate of DLT which refers to MTD

Figure 9 - Mean number of participants per dose level for mTPI2



Abbreviations: H = high rate of DLT, L = low rate of DLT, MTD = maximum tolerated dose, mTPI2 = modified toxicity probability interval 2, T = target rate of DLT which refers to MTD

Figure 10 - Mean number of participants per dose level for 3+3



Abbreviations: H = high rate of DLT, L = low rate of DLT, T = target rate of DLT which refers to MTD

Guo W, Wang SJ, Yang S, Lynn H, Ji Y. Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemp Clin Trials. 2017;58:23-33.

10.12 APPENDIX 12: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

- Contingency procedures are suggested below for an emergency that prevents access to the study site to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.
- During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening, enrollment, and administration of study intervention may be delayed.
- Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.
- Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:
- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data.
- If onsite visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.
- Contingencies implemented due to emergency will be documented.
- The participant may be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs).

10.13 APPENDIX 13: MENUS AND COMPOSITION FOR FOOD EFFECT STUDY

Table 28 - Option 1: Moderate-Calorie, Moderate-Fat Breakfast, Non-Vegan

Item	Qty	U/M	Cals (kcal)	Fat (g)	Prot (g)	Carb (g)
Wheat bread[a]	2	Slice	120	1.0	8.0	22.0
Skippy peanut butter pouch[b]	1	Packet	200	16.0	7.0	6.0
Grape or strawberry jelly[c]	3	Packet	105	0.0	0.0	27.0
Banana, fresh, medium, 7" – 7-7/8"	1	Each	105	0.39	1.29	26.95
2% milk	8	Ounce	130	5.0	8.0	12.0
Total (g)			660	22.39	24.29	93.95
Calories (kcal)			-	201.51	97.16	375.80
Percent by calories			-	29.9%	14.4%	55.7%

Abbreviations: Carb, carbohydrate; Cals, calories; Prot. Protein; Qty, quantity.

a Nature's Own 100% whole wheat bread OR Wonder 100% whole wheat bread.

b A Skippy creamy peanut butter individual packet, 32 g (or measure 1.12 oz out of a jar) OR Jif creamy peanut butter, red cap (measure 1.12 Oz out of a jar).

c A Smucker's individual packet of grape or strawberry jelly, 0.5 oz packet, OR Heinz concord grape or strawberry jelly, 0.5 Oz packet.

Table 29 - Moderate-Calorie, Moderate-Fat Breakfast, Vegan

Item	Qty	U/M	Cals (kcal)	Fat (g)	Prot (g)	Carb (g)
Wheat Bread[a]	2	Slice	120	1.0	8.0	22.0
Skippy Peanut Butter Pouch[b]	1	Packet	200	16.0	7.0	6.0
Grape or Strawberry Jelly[c]	2	Packet	70	0.0	0.0	18.0
Banana, fresh, medium, 7 – 7-7/8"	1	Each	105	0.39	1.29	26.95
Vanilla soy milk, silk[d] / vanilla soy milk, great value[e]	8 / 12	Ounce / Ounce	130 / 133	3.5 / 4.4	6.0 / 8.9	18.0 / 16.3
Total (g)			625	20.89	22.29	90.95
Calories (kcal)			-	188.01	89.16	363.80
Percent by calories			-	29.3%	13.9%	56.8%

Abbreviations: Carb, carbohydrate; Cals, calories; Prot. Protein; Qty, quantity.

a Nature's Own 100% whole wheat bread OR Wonder 100% whole wheat bread.

b Skippy Creamy peanut butter individual packet, 32 g (or measure 1.12 oz out of a jar) OR Jif creamy peanut butter, red cap (measure out of jar 1.12 Oz).

c A Smucker's individual packet of grape or strawberry jelly, 0.5 oz packet OR Heinz concord grape or strawberry jelly, 0.5 oz packet.

d A Silk brand (very vanilla), 8 oz OR Great Value brand (organic vanilla), 12 oz.

e For the vegan option, the total, calories, percent by calories, are based on silk vanilla soy milk.

10.14 APPENDIX 14: ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
ATE:	arterial thromboembolic event
BCRP:	breast cancer resistance protein
BID:	twice daily
BIW:	twice a week
BoR:	best overall response
CBR:	clinical benefit rate
CFR:	Code of Federal Regulations
CI:	confidence interval
CNS:	central nervous system
CPK:	creatinine phosphokinase
CR:	complete response
CRC:	colorectal cancer
CRF:	case report form
CSR:	central serous retinopathy
CT:	computed tomography
ctDNA:	circulating tumor DNA
CYP:	cytochrome P450
DCR:	disease control rate
DL:	dose level
DL1:	dose level 1
DL2:	dose level 2
DL3:	dose level 3
DLT:	dose-limiting toxicity
DoR:	duration of response
DTP:	direct-to-patient
ECG:	electrocardiogram
ECHO:	echocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EOT:	end of treatment
EU:	European Union
FDA:	United States Food and Drug Administration
FDG-PET:	fluorodeoxyglucose positron emission tomography
FSH:	follicle-stimulating hormone
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
GGT:	gamma-glutamyl transferase
GLP:	Good Laboratory Practice
HBsAg:	hepatitis B surface antigen

HBV:	hepatitis B virus
HCV:	hepatitis-C virus
HRT:	hormone replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
ICI:	immune checkpoint inhibitor
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
INR:	international normalized ratio
irAE:	immune-related adverse event
IRB:	Institutional Review Board
IV:	intravenous
LLN:	lower limit of normal
LVEF:	left ventricular ejection fraction
MAPK:	mitogen-activated protein kinase
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose
mTPI:	modified toxicity probability interval
mTPI2:	modified toxicity probability interval 2
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NE:	not evaluable
NF1:	neurofibromin 1
NSCLC:	non-small cell lung cancer
OCT:	optical coherence tomography
ORR:	objective response rate
OS:	overall survival
PD:	progressive disease
PD-1:	programmed cell death protein 1
PD-L1:	programmed death-ligand 1
PDy:	pharmacodynamic
PET:	positron emission tomography
PFS:	progression free survival
P-gp:	P-glycoprotein
PK:	pharmacokinetic(s)
PR:	partial response
PT:	preferred term, prothrombin time
PTT:	partial thromboplastin time
Q3W:	once every 3 weeks
QTcF:	QT interval corrected using Fridericia's formula
RECIST:	Response Evaluation Criteria in Solid Tumours
RP2D:	recommended Phase 2 dose
RPED:	retinal pigment epithelial detachment
RTK:	receptor tyrosine kinase
RVO:	retinal vein occlusion
SAE:	serious adverse event

SD:	stable disease
SHP2:	Src Homology region 2 domain-containing protein tyrosine phosphatase 2
SoA:	schedule of activities
SoC:	standard of care
SUSAR:	suspected unexpected serious adverse reaction
TEAE:	treatment-emergent adverse event
TPS:	tumor proportion score
TTR:	time to response
ULN:	upper limit of normal
UPM:	unit probability mass
VTE:	venous thromboembolic event
WOCBP:	woman of childbearing potential

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amended protocol 03 (29-Mar-2021)

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU).

OVERALL RATIONALE FOR THE AMENDMENT

The following changes need to be implemented into the protocol of TCD16210 study (SHP2/Pembrolizumab combo):

A new POC generating cohort of approximately 40 patients (NSCLC, PD1 naïve) is to be added. This change will result in the changes in the overall study design, schedule of assessments, eligibility criteria, treatment duration, sample size, statistical considerations, laboratory assessments. Safety sections are to be updated in line with most recent information available.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page and Section 1.1 (Synopsis)	Protocol title and short title were updated	A new POC generating cohort (Part-2) of 40 patients (NSCLC, PD1 naïve) has been added
Section 1 (PROTOCOL SUMMARY) and Synopsis	Disclosure Statement: has been updated from "This is a single arm treatment" to "This is a two-parts treatment study".	Section 1 (PROTOCOL SUMMARY) and Synopsis

Section # and Name	Description of Change	Brief Rationale
Section 2 (INTRODUCTION)	Section 2.1 (STUDY RATIONALE) has been updated with new information and rationale of adding new cohort. New Section 2.2.1 (Rationale for NSCLC) was added with information on NSCLC population. New Section 2.2.2 (Current standard of care in NSCLC) was added with current standard of care for NSCLC. New Section 2.2.3 (Rationale for combining SAR442720 with pembrolizumab) was added with rationale for combining SAR442720 with pembrolizumab.	Overall study design, schedule of assessments, eligibility criteria, treatment duration, sample size, statistical considerations, laboratory assessments, and. safety sections were adjusted to accommodate Part-2 of the study.
	Section 2.3 (BENEFIT/RISK ASSESSMENT) was updated with new information on benefits assessment, COVID-19 risk assessment section and with a new table on potential risks of SAR442720.	Risk assessment strategies for COVID-19 related disruptions were added.
Section 3 (OBJECTIVES AND ENDPOINTS)	Objectives and endpoints table was updated with new Part-2 of the study.	Overall study design, objectives and endpoints were adjusted to accommodate Part-2 of the study.
Section 4 (STUDY DESIGN)	Section 4.1 (OVERALL DESIGN) was updated with new Part-2 of the study. Section 4.2 (SCIENTIFIC RATIONALE FOR STUDY DESIGN) was updated with scientific rationale for Part-2 of the study. Section 4.3 (JUSTIFICATION FOR DOSE) was updated with SAR442720 and pembrolizumab doses for Part-2 of the study. Section 4.4 (End of study definition) was updated with new definition.	Overall study design, schedule of assessments, eligibility criteria, treatment duration, sample size, statistical considerations, laboratory assessments, and. safety sections were adjusted to accommodate Part-2 of the study.
Section 5 (STUDY POPULATION)	Section 5.1 (INCLUSION CRITERIA): the inclusion criteria, I8, I9, I10, and I11 for Part-2 were added. Section 5.2 (EXCLUSION CRITERIA) was rearranged, exclusion criteria E1 was corrected for typo, E3 was updated, E4 was deleted for conciseness and clarity, present E12 & E17 were updated for clarity, present E22 was refined due to emerging safety data, previous E19 was deleted, present E19 was added, and the exclusion criterion for Part-2 of the study was added.	
Section 6 (STUDY INTERVENTION)	Section 6.1 (Table-10) was updated with the dose of pembrolizumab for Part-2. Section 6.5 (CONCOMITANT THERAPY) was updated with the treatment of direct Factor X inhibitors and LMWH. Section 6.5.1 (Prohibited concomitant therapy) was updated with newly allowed therapies. Section 6.6 (DOSE MODIFICATION) was updated with dose modification criteria for Part-2. Section 6.6.1.1 (management of diarrhea) was additionally updated with alternative medicines in order to treat diarrhea. Section 6.7 (INTERVENTION AFTER THE END OF THE STUDY) was updated with deletion of definition of end of study.	

Section # and Name	Description of Change	Brief Rationale
Section 7 (DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITH DRAWAL)	Section 7.1.2 (Temporary discontinuation) was updated with information on COVID-19 related disruptions.	
Section 8 (STUDY ASSESSMENTS AND PROCEDURES)	Section 8.1 (EFFICACY ASSESSMENTS) was updated with modification of Part-1 assessments and addition of Part-2 assessments. Section 8.3.4 (Regulatory reporting requirements for SAEs) was updated with suggested texts included in the recent template. Section 8.6 (PHARMACODYNAMICS) was updated with Part-2 sample collections. Section 8.7 (GENETICS) was updated with baseline blood sample collections from consenting participants. Section 8.8 (BIOMARKERS) was updated with new sample collection procedures. New Section 8.11 (USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH) was added.	
Section 9 (STATISTICAL CONSIDERATIONS)	Section 9.1 (STATISTICAL HYPOTHESES) was updated with statistical hypotheses related to Part-2 of the study. Section 9.2 (SAMPLE SIZE DETERMINATION) was updated with sample sizes of Part-1 and Part-2 and a new table of estimated objective response rate (ORR) was added. A "Note" for enrolled participants is deleted. Section 9.3 (Population for analyses) was updated with the description for “Enrolled”. Section 9.4.1 (General considerations) was expanded with new information on analysis period. Section 9.4.2 (Efficacy endpoints) was updated with an expanded table on efficacy end points and end point definitions. Primary endpoint(s)' was changed to "efficacy endpoints'. Section 9.4.3 (Secondary endpoints) was changed to “Safety endpoints” and further subsections related to safety were added. New Section 9.4.3.1 (Adverse events) was added and updated with list of adverse events. Section 9.4.4 (other endpoints) was updated with information on the presentation of data. Section 9.5 (INTERIM ANALYSES) was updated stating that no interim analyses were planned.	

Section # and Name	Description of Change	Brief Rationale
Section 10 (SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS)	Section 10.5 Appendix 5 (GENETICS) was updated with new information on DNA analysis. Section 10.9 Appendix 9 (GENERAL GUIDELINES FOR THE MANAGEMENT OF IMMUNE RELATED ADVERSE EVENTS) Dose modification outlines in Table-19 were extensively updated for clarity. New Section 10.12 Appendix 12 (CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY) was added with information on COVID-19 disruptions. Section 10.14 Appendix 14 (PROTOCOL AMENDMENT HISTORY) was updated with changes in last protocol amendment.	Contingency measures were included for unintended disruptions.
Section 11 (Reference)	Section 11 was updated with new references.	

Amended protocol 02 (02-Jul-2020)

This amended protocol (amendment 02) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU) because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol was amended to allow an alternative twice a week (BIW) dose schedule. Additional changes and clarifications are summarized below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis (Secondary endpoints and Statistical consideration) Section 3 Objectives and Endpoints	Best overall response (BoR) was replaced with duration of response (DoR) in a secondary endpoint. DoR was removed from the list of the tertiary/exploratory endpoints.	Duration of response is a clinically important endpoint that is related to quality of life. BoR will be summarized in this study.
Section 1.1 Synopsis (Overall study design, Intervention groups and duration) Section 4.1 Overall Design Section 4.3 Justification for Dose	"Day 1, Day 4" was replaced with "BIW" where needed throughout the text and tables. The text regarding the starting dose of SAR442720 was edited. The following text were added for clarity: "During the study, alternative BIW dose schedules, such as Day 1 and Day 2 of each week, or any other emergent dose schedule from the ongoing Phase 1 monotherapy escalation study can be explored after agreement of the Study Committee." "The decision to initiate alternative dose levels will be made by the Study Committee after careful evaluation of safety and/or PK data from the ongoing Phase 1 monotherapy escalation study and data generated in this combination study."	Emergence of an alternative, tolerable dose schedule.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis (Overall study design) Section 4.1 Overall Design Section 10.1.5 Committee structure	The following text was added: "the safety and/or PK data observed in the ongoing Phase 1 monotherapy escalation study"	Emergence of an alternative, tolerable dose schedule.
Section 1.2 Schema	Figure 1 title updated from: "Graphical study design" to "Graphical study design of SAR442720 administered on Day 1 and Day 4 Pembrolizumab every 3 weeks".	Clarification
	Figure 1 "SAR442720 (Oral Day 1, Day 4 weekly per cycle)" replaced with "SAR442720 (Oral BIW per cycle)"	To be consistent with the addition of Day 1, Day 2 or any other potential schedules that may emerge.
Section 1.3 Schedule of Activities Section 10.2 Appendix 2	The following text was added for laboratory assessments (including liver chemistries): "C2+Day 15 laboratory assessments could be done remotely if needed and after discussion with the Study Medical Manager."	Clarification
Section 1.3 Schedule of Activities, Table 2	Additional pharmacokinetic (PK) sample collection time points were added for participant receiving SAR442720 on the Day 1, Day 2 of each week dosing schedule.	To monitor the concentrations of SAR442720 in Day1, Day 2 of each week dosing schedule.
Section 1.3 Schedule of Activities, Table 3	Separate row for Cycle 2 assessments has been deleted and combined with Cycle 3 and 4 rows.	Clarification.
Section 2.3.1 Risk assessment	The following statement was removed: "Phototoxicity studies with SAR442720 have not been completed. Therefore, participants taking SAR442720 should use appropriate protection when exposed to UV radiation"	In vitro and in vivo studies have been conducted and no indication of phototoxicity was observed. This information is included in the SAR442720 Investigator's Brochure (IB) v3.
	The following text, "approximately 6.4x of unbound C_{max}", was adjusted to "approximately 17x of unbound C_{max}".	Clarification.
	The following paragraph was added: "Emerging data from ongoing studies identifies anemia as a new potential risk based on clinical data and preclinical evidence. In the monotherapy study (n=82), anemia AEs (Standardized MedDRA Query [SMQ]), of any grade, were reported in 26 (31.7%) participants, including 11 (13.4%) participants who required blood transfusions. Grade 3 anemia events were reported in 13 (15.9%) participants; 3 SAE including 1 event related to study drug. No Grade 4 anemia events have been reported to date. Median time to onset of anemia was 22 days from the start of study treatment, and median time to recovery was 21 days. In addition, 54 (65.9%) participants had a hemoglobin grade shift from baseline, of which 27 participants were anemic at baseline, among which 3 (3.7%) participants had a hemoglobin shift from Grade 1 to Grade 3 and 5 (6.1%) participants had a hemoglobin shift from Grade 2 to Grade 3. The other 27 participants were normal at baseline, among which 6 (7.3%) participants had a Grade 2 worsening and 2 (2.4%) participants had a Grade 3 worsening."	Anemia is the third risk which has been identified as potential risk. It was added to the protocol as to alert the investigators.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1 Dose-limiting toxicity criteria	Deleted "or hemorrhage" from following bullet point "Grade 3 neutropenia lasting >7 days or febrile neutropenia or hemorrhage"	Correction
	The following dose-limiting toxicity (DLT) criterion was updated from: • "Grade 3 non hematologic AEs, including rash, nausea/vomiting, hypertension, diarrhea, that remain uncontrolled for >72 hours despite maximal supportive care. Electrolyte abnormalities or Grade 3 asymptomatic CPK or GGT elevations that is corrected within 72 hours will not be considered DLTs." To: • "Grade 3 nonhematologic AEs, including rash, nausea/vomiting, hypertension, diarrhea, retinopathy, or blurred vision that remain uncontrolled (does not resolve to ≤ Grade 2) for >72 hours despite maximal supportive care. Electrolyte abnormalities or Grade 3 asymptomatic CPK or GGT elevations that are corrected within 72 hours will not be considered DLTs."	The changes were made to reflect the CTCAE definition of these events. Retinopathy was added as a DLT criteria and will comprise retinal detachment.
	The following DLT criterion was deleted: • Grade 3 retinal detachment, tear or vascular disorder	Not an observed AE for this molecule according to the ongoing monotherapy study codes.
Section 4.3 Justification for dose	The human Ether-à go-go (hERG) safety margin-related details have been updated. The sentence changed from: "The unbound steady state maximum plasma concentration ($C_{max,u}$) at 140 mg and 200 mg via D1-D4 schedule provides adequate hERG safety margin (9.4x for 140 mg and 6.4x for 200 mg dose)." To: "The unbound steady state maximum plasma concentration ($C_{max,u}$) at 140 mg Day 1, Day 4 and 200 mg BIW (Day 1, Day 4 and Day 1, Day 2) schedule provides an adequate hERG safety margin (≥17x)."	Clarification based on IB v3.
Section 5.2 Exclusion criteria	Deleted "…and PI3K δ inhibitors" from exclusion criterion E 09. The following text was added to the 3rd bullet point of exclusion criterion 23: "…during the dose escalation portion of the study". Exclusion criterion E 24 sub-bullet was corrected from "…creatinine clearance of >50 mL/min" to "…creatinine clearance of <50 mL/min" The following text was added to the 7th bullet point of exclusion criterion 24: "or outside the therapeutic range of the local laboratory if receiving therapeutic anticoagulation that would affect the PT/INR".	Corrections

Section # and Name	Description of Change	Brief Rationale
Section 6.5.1 Prohibited concomitant therapy	The following text was added to the 5th and 6th bullet points:"…(only during the dose escalation portion of the study)"	Clarification
Section 6.6.1.1 Management of diarrhea	"Lomotil" was added for treatment of Grade 1 or 2 diarrhea.	Clarification
Section 6.7 Intervention after end of the study	Additional details were added and text updated from: "Participants who continue to receive study intervention at the end of the study and are deriving clinical benefit from SAR442720 and pembrolizumab will be considered for enrollment in a separate extended use or roll over study." To: "Participants who continue to receive study intervention at the end of the study and are deriving clinical benefit from SAR442720 and pembrolizumab may receive study intervention until disease progression, an unacceptable AE, or the participant's or Investigator's decision to stop the treatment. The end of the study is defined as the date of the last visit of the last participant in the study or 12 months after last participant is enrolled, whichever occurs first. The participant's treatment after the end of the study will be at discretion of treating physician."	Clarification of study intervention at the end of the study.
Section 7.1.1 Definitive discontinuation	Following additional text was added: "During the conduct of the study, in cases where premature discontinuation of SAR442720 is required, the participant may continue pembrolizumab treatment, upon Investigator decision and in agreement with the Study Medical Manager. Likewise, in cases where premature discontinuation of pembrolizumab is required, the participant may continue SAR442720 treatment if there is presence of, or potential for, clinical benefit as assessed by the Investigator and Study Medical Manager."	Clarification of administration of investigational medicinal products in case of discontinuation of one drug.
Section 8.2.2 Vital signs	The duration of rest before vital signs are measured was adjusted ("5 to 10 minutes").	Clarification.
	Following text was deleted: "Vital signs include: temperature, blood pressure preferably in seated position after at least 10 minutes of rest, pulse rate, pulse oximetry, and respiratory rate"	Duplicated of information and hence deleted.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.7 Retinal examinations	Retinal examination details were updated from: "Retinal examinations performed by an ophthalmologist are required during this study as described in the SoA (Section 1.3). Examinations should include visual acuity, dilated retinal examinations, and optical coherence tomography (OCT) to evaluate the retinal pigment epithelium. Additional tests, such as fluorescein angiography, may be utilized to monitor leakage and inflammation related side effects." To: "Retinal examinations performed by an ophthalmologist are required during this study as described in the SoA (Section 1.3). Examinations include best-corrected visual acuity including pinhole vision if indicated, dilated funduscopic examinations, and macular and optical coherence tomography (OCT). Additional tests, such as fluorescein angiography, may be utilized to monitor leakage and inflammation-related side effects."	Clarification on the proposed retinal examination.
Section 9.4.3.2 Objective response rate (ORR) and duration of response (DoR)	In alignment with the changes made in Section 3 to objectives and endpoints, the following description of ORR and DoR has been added and text regarding BoR has been reduced: "Objective response rate is defined as the proportion of participants who achieve a CR or PR per RECIST v1.1. Objective response rate and the corresponding 90% 2-sided CI will be derived. CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (refer to Section 8.1 for imaging assessment instructions). Best overall response per RECIST v1.1 will also be summarized. Duration of response (DoR) per RECIST v1.1 is defined as the interval from the first documentation of complete response (CR) or partial response (PR) to the earlier of first documentation of definitive disease progression or death due to any cause, whichever occurs first. Participants who are still alive and free from progression at the time of data cutoff date, are lost to follow-up, have discontinued from the study, or who have initiated subsequent anticancer therapy will be censored at the last adequate tumor assessment. For participants who achieve CR or PR, the Kaplan-Meier curve will be generated. The Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and their associated 95% CI will be provided."	To be consistent with BoR replacement with DoR as a secondary endpoint.
Section 9.4.4 Other endpoint(s)	"DoR per RECIST v1.1" has been deleted	DoR is now covered as a secondary endpoint in Section 9.4.3.2.

Section # and Name	Description of Change	Brief Rationale
Section 10.9 Appendix 9, Table 14. Dose modification guidelines	Following new AEs and pertaining action has been added: Colitis, Nephritis, Endocrinopathies, Other immune-related adverse reactions, and Pembrolizumab Infusion-related reactions. Adverse event term of "Rash" changed to "Skin Reactions" and corresponding action has been updated. Added AE of "Hepatitis" along with other liver function test abnormalities and corresponding action has been updated.	Dose modification guidelines were amended based on health authority feedback.
Throughout	Typos have been corrected where necessary.	Clarifications
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amended protocol 01 (06-Mar-2020)

This amended protocol (amendment 01) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

Overall rationale for the amendment

The protocol received comments from the US FDA regarding the DLT criteria and inclusion criteria. The revisions made are owing to the FDA suggestions as summarized below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1 Dose limiting toxicity criteria	Added neutropenia lasting longer than 7 days as a potential DLT	As requested by health authorities
Section 4.1.2 Dose escalation	Added experiencing a DLT in the DLT observation period to be evaluable for DLT assessment	As requested by health authorities
Section 4.2.1 Dose escalation rationale	Modified the design such that at no point will the upper limit of the probability of toxicity be >33%	As requested by health authorities
Section 5.1 Inclusion criteria	Modified I02	As requested by health authorities

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