NCT: NCT04418661

STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 1/2, open-label, multicenter, dose escalation and dose expansion study of SAR442720 in combination with other agents in patients with advanced malignancies**
Protocol number:	**TCD16210**
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**
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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study SAR442720 TCD16210 is based on the protocol dated 26-Oct-2021. This section summarizes major changes to the statistical analysis features in the SAP. This SAP is approved before database lock of the expansion cohort.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0		This is the original version of SAR442720 TCD16210 SAP.	

1 INTRODUCTION

1.1 STUDY DESIGN

Part-1

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

The Phase 1 safety study is to characterize the safety and tolerability of SAR442720 in combination with pembrolizumab and to confirm the recommended Phase 2 dose (RP2D). Participants with either NSCLC or advanced CRC will be enrolled in the study. There is no minimum patient number requirement for either tumor type.

There are 3 scheduled dose levels in the consideration: the starting dose (DL 1) of SAR442720 (140 mg BIW), dose level 2 (DL2) (200 mg BIW) and DL-1 (100 mg BIW). The DLT observation period is 1 cycle (21 days). The Study Committee will review the overall safety, PK/PD and preliminary antitumor activity data and will decide the recommended dose for the expansion phase.

Part-2

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

Part-2 will assess the antitumor 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 at the RP2D for SAR442720 defined in Part-1. The SAR442720 RP2D will be 200 mg BIW, such Day 1 and Day 2 of each week, administered orally (21 days per cycle). Pembrolizumab will be administrated as a dose of 200 mg using 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 ever 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 of the study will investigate the safety and tolerability of SAR442720 in combination with adagrasib and confirm RP2D. There are 6 dose levels in consideration: the starting dose (dose level 1 [DL1]) of IMP combination will be 100 mg BIW and 400 mg BID for SAR442720 and adagrasib respectively, dose level 2 (DL2) will be 140 mg BIW and 400 mg BID, dose level 3a (DL3a) will be 140 mg BIW and 600 mg BID, dose level 3b (DL3b) will be 200 mg BIW and 400 mg BID, dose level 4 (DL4) will be 200 mg BIW and 600 mg BID, and dose level (-)1 ([DL-1]) will be 80 mg BIW and 400 BID. A minimum of 3 DLT evaluable participants for each dose level is required. The DLT observation period is 1 cycle (21 days). 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.

Part-3B dose expansion will assess the anti-tumor activity and safety of SAR442720 combined with adagrasib in participant with NSCLC harboring KRAS G12C mutation. This study will start once RP2D for SAR442720 and adagrasib from Part-3A dose escalation is confirmed. Approximately 40 participants will be enrolled.

Part-4 of this study will assess the effect of food on 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 capsule formulation (reference) when dosed in combination with pembrolizumab. Approximately 12 participants are expected to be enrolled.

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Part-1

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability for the combination of SAR442720 and pembrolizumab in participants with advanced solid tumors including 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) Version 5.0 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 document the pharmacokinetic (PK) for the combination of SAR442720 and pembrolizumab, and to document the PK of pembrolizumab in combination with SAR442720	• Plasma concentrations of SAR442720 • Serum concentrations of pembrolizumab
• To estimate the anti-tumor effects for the combination of SAR442720 and pembrolizumab in all participants	• Objective response rate (ORR) and duration of response (DoR) for the combination therapy 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

Objectives	Endpoints
Primary	
• To determine the antitumor 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 investigator per RECIST v1.1
Secondary	
• To assess the safety profile of SAR442720 in combination with pembrolizumab	• Incidence of TEAEs, SAEs, laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0
• To assess other indicators of antitumor 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 investigator per RECIST v1.1 (for NSCLC) • DoR, defined as the time from first documented evidence of CR or PR until progressive disease (PDdetermined by investigator per RECIST v1.1 or death from any cause, whichever occurs first • Clinical benefit rate (CBRincluding confirmed CR or PR at any time or stable disease (SD) of at least 6 months determined by 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 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

Objectives	Endpoints
Primary	
• To define the MTD and RP2D for the combination of SAR442720 and adagrasib in participants with NSCLC and KRASG12C mutations	• Incidence of study drug-related DLTs in Cycle 1
Secondary	
• To characterize the safety and tolerability of SAR442720 in combination with adagrasib in participants with NSCLC and KRASG12C mutations	• Incidence, nature, and severity of treatment emergent AEs and SAEs, graded according to the NCI CTCAE Version 5.0 for the combination of SAR442720 and adagrasib
• 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 • PK parameters of adagrasib

Objectives	Endpoints
• 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

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR442720 in combination with adagrasib in participants with NSCLC and KRASG12C mutations	• Objective response rate defined as the proportion of participants who have a confirmed CR or PR determined by investigator per RECIST v1.1
Secondary	
• To assess the safety profile of SAR442720 when combined with adagrasib in participants with NSCLC and KRASG12C mutations	• Incidence of TEAEs, SAEs, laboratory abnormalities according to NCI CTCAE V5.0
• To assess other indicators of antitumor 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 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 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 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 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-3 (Part-3A and Part-3B)

Objectives	Endpoints
Tertiary/exploratory	
[redacted]	[redacted]

Part-4

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 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, when dosing with capsule and tablet formulations in combination with pembrolizumab	• Incidence, nature, and severity of treatment emergent AEs and SAEs, graded according to the NCI CTCAE Version 5.0 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

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 patients need to be treated at the MTD. After MTD is identified, another 6 patients will be treated at the MTD to confirm the decision and determine the RP2D. Therefore, a range of 18-24 DLT-evaluable (defined in Section 3) patients 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 patients in Cohort A1 with PD-L1 TPS>=50% and 20 patients in Cohort A2 with PD-L1 TPS in 1-49%, will be enrolled at the RP2D identified from the Part-1. 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.

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

Part-3B, 40 participants will be enrolled at the RP2D identified from the Part-3A. With a sample size of 40 study participants in each cohort of 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.

Part 4, 12 participants are expected to be enrolled in each group. By assuming AUC single dose Coefficient of Variation is [redacted], 12 participants in each group will achieve a maximum imprecision of [redacted]. When the AUC ratio is[redacted], the 90% CI would be [redacted] respectively. When 9 participants are PK evaluable in each group, the maximum imprecision would be[redacted]. When the AUC ratio is[redacted], the 90% CI would be [redacted] respectively.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
Enrolled	All participants who sign the ICF and have dose allocated to an intervention regardless of whether the intervention was received or not.
DLT-evaluable (only for Part-1 and Part-3A)	Patients who take at least 4 of the 6 planned doses of SAR442720 (Part-1 and Part-3A) and 28 of the 42 planned doses of adagrasib (Part-3A) in the first cycle of the treatment and complete the DLT observation period. OR Patients who have any DLT observed in the DLT observation period.
PK	Patients who have at least one measurable SAR442720 concentration or at least one measurable pembrolizumab concentration after the first dose or at least one measurable adagrasib concentration after the first dose.
PD	Patients who have at least one PD marker result after the first dose
Safety	Patients who take at least one dose of any IMP (i.e., SAR442720, pembrolizumab, or adagrasib)
PK evaluable (Part-4 only)	Patients who complete all of cycle 1 and C2D1 with meal information, full PK, and no dose reduction/missed doses on C1D1, C1D15 and C2D1. Missing some PK samples may still be considered as evaluable and will be assessed case-by-cased.

Abbreviations: DLT = dose-limiting toxicity, ICF = informed consent form, PD = pharmacodynamic(s), PK = pharmacokinetic(s)

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SDs), median, [Q1, Q3,] minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of investigational medicinal product (IMP). The MTD recommendation and DLT summary will be based on the DLT-evaluable population Cycle 1 data only excluding the 6 patients in the mini-expansion. All safety and efficacy analyses will be based on the safety population unless otherwise specified. The Part-1 and Part-2 analyses will be performed separately unless specified otherwise. Part-1 analyses will be presented by different dose levels, and Part-2 analyses will be presented by cohorts defined by different PD-L1 TPS. Part-3A analyses will be presented by dose levels, and Part-3B analyses, unless otherwise specified, will be presented overall. Part-4 analyses will be presented overall.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **on-treatment period** (ie, treatment-emergent [TE] period) is defined as the period from the first IMP administration to the last IMP administration + 30 days.
- The **post-treatment period** is defined as the period from the end of the on-treatment period. [After last IMP administration + 31 days]

4.2 PARTICIPANT DISPOSITIONS

The number (and percentage) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently dosed. The number (and percentage) of screen failures and reasons for screen failures will be provided.

Regarding intervention discontinuation, the following definitions will be used:

- Permanent **full** intervention discontinuation is defined as the discontinuation of all the study drugs

The number (and percentage) of participants in the following categories will be provided:

- Enrolled population
- Safety population

- DLT evaluable population (only for Part-1 and Part-3A)
- Pharmacokinetics population
- Pharmacodynamic population
- Participants who did not complete the study treatment as per protocol and main reason for full treatment discontinuation and treatment withdrawal by subject
- Participants who did not complete study/follow-up period as per protocol and main reason for study discontinuation
- Subject survival status

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the safety population.

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 endpoints for Part-2, Part-3B, and Part-4.

All AEs will be graded according to National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) version 5.0 and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the on-treatment period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the deaths will be analyzed in the on-treatment and post-treatment periods. The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity/grade is missing for one of the treatment-emergent occurrences of an AE, the severity/grade will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity/grade will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. Summaries will be provided for all grades combined and for grade ≥3 (including Grade 5). Missing grades, if any, will be included in the "all grades" category.

The AE tables will be sorted as indicated in Table 4.

Table 4 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the overall incidence

Analysis of all adverse events

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

- TEAEs
- Any grade >= 3 TEAE
- Any treatment emergent SAE
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period or all-cause mortality)
- Serious TEAEs
- Serious treatment-related TEAEs.
- TEAE leading to premature discontinuation of either SAR442720 or pembrolizumab or adagrasib
- TEAE leading to permanent full intervention discontinuation (definitive discontinuation)
- TEAE leading to dose modifications
- Treatment-related TEAEs
- Treatment-related TEAEs of grade >= 3
- AESI
- DLTs

The AE summaries of participants experiencing TEAEs by primary SOC and preferred term will be generated with number (%) of participants experiencing at least one event in Table 5. The analyses will be performed for all grades combined and for grades ≥3 according to NCI CTCAE v5.0. 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.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, and PT
TEAE related to SAR442720 as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to SAR442720 as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE related to pembrolizumab as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE related to adagrasib as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent full intervention discontinuation	Primary SOC and PT
TEAE leading to permanent discontinuation of SAR442720	Primary SOC and PT
TEAE leading to permanent discontinuation of pembrolizumab	Primary SOC and PT
TEAE leading to permanent discontinuation of adagrasib	Primary SOC and PT
TEAE leading to death	Primary SOC and PT
TEAE leading to dose modification (including dose delay, dose reduction and dose omission) of SAR442720	Primary SOC and PT

Analysis of deaths

The deaths will be summarized by observation period ie, number (%) of deaths during the on-treatment period and number (%) of deaths during post-treatment period.

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) in Section 8.3.7 of protocol amendment 4 will be selected for analyses as indicated from CRF. Number (and percentage) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 4.

4.4 EFFICACY ENDPOINT(S)

Efficacy endpoints involved in this study are summarized in the following table (Table 6).

Table 6 - Summary of efficacy endpoints

Efficacy Endpoint	Part-1/3A	Part-2/3B	Part-4
ORR per RECIST 1.1	Secondary	Primary	Secondary
DoR	Secondary	Secondary	Secondary
PFS	NA	Secondary	NA
TTR	NA	Secondary	NA
CBR	NA	Secondary	NA
OS	NA	Exploratory	NA
ORR per iRECIST	NA	Exploratory	NA

The Best Overall Response (BOR) by RECIST 1.1 will be summarized. The Objective Response Rate (ORR) by RECIST 1.1 is calculated as the proportion of participants with BOR as Complete Response (CR) or Partial Response (PR). The 90% two-sided confidence interval for ORR will be computed using the Clopper-Pearson method.

The primary analysis using the Objective Response Rate (ORR) is performed when all participants have at least 2 post baseline tumor assessments with response durability demonstrated or discontinued study treatment (whichever occurs first). ORR is defined as proportion of participants who have confirmed complete response (CR) or partial response (PR) determined by investigator per RECIST v1.1. The 90% CI is estimated using Clopper Pearson method.

The BOR of CR or PR needs to be confirmed by a subsequent assessment. BOR per RECIST 1.1 will be summarized. Waterfall plot will be generated for the best change from baseline for target lesions for each participant.

Duration of response (DoR) according to RECIST v1.1 will be summarized. The DoR will be defined as the time interval from the date of the first occurrence of CR or PR that is subsequently confirmed (eg, in case of a patient who has four assessments as PR SD PR PR, the second PR date will be used for the calculation) to the date of the first documentation of disease progression or death due to disease progression, 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 detailed censoring rules are listed in Table 7 below. DoR will be analyzed for responders using Kaplan-Meier methods and following estimates will be provided:

- Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 90% CIs will be provided. The 90% CIs will be constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley.
- Number of patients at risk as well as the probabilities of being event-free at least 2, 4, 6, 8, 10 and 12 months with 90% CIs will be estimated using the Kaplan-Meier method and a log-log approach based on a normal approximation following the Greenwood's formula.
- Kaplan-Meier curves will be plotted. These plots will include the number of patients at risk at key time points.

In addition, number (and percentage) of events and patients censored will be presented with type of events and reason of censoring.

Table 7 - DoR analysis - Event and censoring rules

Situation	Date of outcome	Outcome	Category
Ongoing and no documented progression	Date of the last evaluable tumor assessment documenting no progression	Censored	Ongoing without progression
Documented progression (or Death) at or between scheduled visits	Date of progression (or Date of death)	Event	Documented progression (or Death without documented progression)
Documented progression (or Death) occurring after two or more non-evaluable tumor assessment[a]	Date of the last evaluable tumor assessment documenting no progression	Censored	Event occurred after two or more missed tumor assessment
Initiation of further anti-cancer therapy	Date of the last evaluable tumor assessment before start date of further anti-cancer therapy	Censored	Initiation of further anti-cancer therapy

a An event occurring at least 19 weeks (excluded) after the last evaluable tumor assessment

Progression Free Survival (PFS) per RECIST v1.1 is defined as the time from the date of the first IMP administration of to 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 detailed censoring rules are listed in the Table 8 below. PFS will be analyzed using Kaplan-Meier methods and following estimates will be provided:

- Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 90% CIs will be provided. The 90% CIs will be constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley.
- Number of patients at risk as well as the probabilities of being event-free at least 2, 4, 6, 8, 10 and 12 months with 90% CIs will be estimated using the Kaplan-Meier method and a log-log approach based on a normal approximation following the Greenwood's formula.
- Kaplan-Meier curves will be plotted. These plots will include the number of patients at risk at key time points.

In addition, number (%) of events and patients censored will be presented with type of events and reason of censoring.

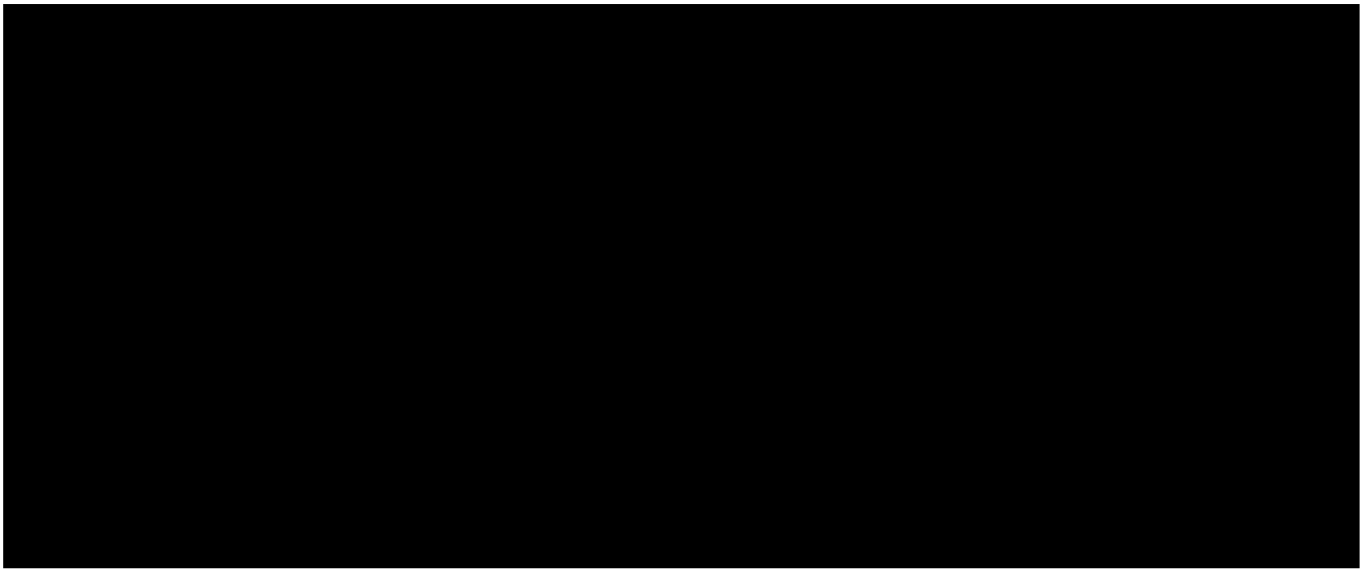
Table 8 - PFS analysis - Event and censoring rules

Situation	Date of outcome	Outcome	Category
No baseline tumor assessments	Date of first dose	Censored	No baseline tumor assessments
No evaluable post-baseline tumor assessments	Date of first dose	Censored	No evaluable post-baseline tumor assessments
Ongoing and no documented progression	Date of the last evaluable tumor assessment documenting no progression	Censored	Ongoing without progression
Documented progression (or Death) at or between scheduled visits	Date of progression (or Date of death)	Event	Documented progression (or Death without documented progression)
Documented progression (or Death) occurring after two or more non-evaluable tumor assessment[a]	Date of the last evaluable tumor assessment documenting no progression	Censored	Event occurred after two or more missed tumor assessment
Initiation of further anti-cancer therapy	Date of the last evaluable tumor assessment before start date of further anti-cancer therapy	Censored	Initiation of further anti-cancer therapy

a An event occurring at least 19 weeks (excluded) after the last evaluable tumor assessment

Time to response (TTR) is defined as the time 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 (CBR) 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.



[redacted]

4.6 MULTIPLICITY ISSUES

There is no formal statistical test performed. Therefore, no multiplicity issue applies.

4.7 OTHER SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 3, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.

4.7.1 Extent of exposure

4.7.1.1 Overall exposure

The dose information will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of any study interventions is administered.
- Duration of IMP exposure (in weeks) is defined as (Last day of exposure – first day of exposure +1)/7.
- The first day of exposure is defined as the first administration date with non-zero dose for at least one of the IMP.

  The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the maximum between:

  - The last administration date + 3 for SAR442720

    The last administration date + 20 for Pembrolizumab given at 200 mg IV Q3W or + 41 for Pembrolizumab given at 400 mg IV Q6W

The total number of cycles started will be summarized as a quantitative variable and by category (1-3 cycles, 4-6 cycle, ..., ≥16 cycles). The duration of overall exposure will be summarized quantitatively.

4.7.1.2 SAR442720 exposure

The dose information will be assessed by the following:

- Number of doses
- Number of cycles started per participant
- Duration of SAR442720 exposure (in weeks) is defined by (date of last administration of SAR442720 + 3 – date of first administration of SAR442720 + 1)/7
- Actual dose (mg)
- Cumulative dose (mg): the cumulative dose is the sum of all actual doses of SAR442720, given from first to last administration
- Actual dose intensity (ADI in mg/week): defined as the cumulative dose divided by the duration of SAR442720 exposure (in weeks)
- Planned dose intensity (PDI in mg/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 3weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

The total number of doses, number of cycles started by participant will be summarized as a quantitative variable and by category (1-3 cycles, 4-6 cycle, ..., ≥16 cycles). Duration of SAR442720 exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications:

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent SAR442720 administrations, dose reduction will be determined by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards. “Not taken” information from eCRF dosing page to be taken into account to identify dose omissions.
- Dose delay: a dose is deemed to have been delayed if the dose is administrated up to 3 days after the theoretical date

Dose modifications will be analyzed by participant, cycle and dose as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose reduction
  - Number (%) of participants with at least 1 dose omission

- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose reduction
  - Number (%) of cycles with at least 1 dose omission

4.7.1.3 Pembrolizumab exposure

The dose information will be assessed by the following:

- Number of doses
- Number of cycles started per participant
- Duration of pembrolizumab exposure (in weeks) is defined by (date of last administration of pembrolizumab + 20 (200mg IV Q3W) or 41 (400mg IV Q6W) – date of first administration of pembrolizumab + 1)/7
- Actual dose (mg)
- Cumulative dose ([mg]): the cumulative dose is the sum of all actual doses of pembrolizumab, given from first to last administration
- Actual dose intensity (ADI in mg/week): defined as the cumulative dose divided by the duration of pembrolizumab exposure (in weeks)
- Planned dose intensity (PDI in mg/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 3weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

The total number of doses, number of cycles started by participant will be summarized as a quantitative variable and by category (1-3 cycles, 4-6 cycle, ..., ≥16 cycles). Duration of pembrolizumab exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications:

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent pembrolizumab administrations, dose reduction will be determined by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards. “Not taken” information from eCRF dosing page to be taken into account to identify dose omissions.
- Dose delay: a dose is deemed to have been delayed if the dose is administrated up to 3 days after the theoretical date.

- Dose interruption and the reason of interruption (as collected in the eCRF). Dose will be considered interrupted if the administration is stopped during the infusion before it is completed regardless of whether it is restarted.

Dose modifications will be analyzed by participant, cycle and dose as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose reduction
  - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with at least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose reduction
  - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

4.7.2 Laboratory variables

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters.

A summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade≥ 3 abnormal laboratory tests occurring during on-treatment period. For patients with multiple occurrences of the same laboratory variable during the treatment, the maximum grade (worst) per patient will be used. The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period. For laboratory tests for which NCI-CTCAE V5.0 scale is not applicable, the frequency of evaluable patients outside normal ranges will be provided.

If relevant, selected laboratory tests will be plotted describing mean changes from baseline and associated +/- STD throughout the on-treatment period.

4.7.3 Additional safety analyses (Vital signs and electrocardiograms [ECGs])

The following vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Vital signs: heart rate, systolic and diastolic blood pressure, weight, pulse rate, respiratory rate, pulse oximetry, and ECOG performance status
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Bazett/Fridericia)/ECG assessments will be described as normal or abnormal

For vital sign variables, potentially clinically significant abnormalities (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. PCSA criteria will determine which participants had

at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The incidence of PCSA any time during the on-treatment period will be summarized.

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

4.8 OTHER ANALYSES

4.8.1 PK analyses

Concentrations of SAR442720, pembrolizumab and adagrasib will be summarized by scheduled visit and nominal timepoint.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics excepted for the geometric mean and associated coefficient of variation for which they will be considered as missing.

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:

- Maximal concentration: Cmax (observed)
- Time to reach maximal concentration: Tmax (observed)
- Area-under-the-curve from time 0 to t: AUC0-t
- Area-under-the-curve from time 0 to infinity, if possible: AUC0-inf, if possible
- t1/2, 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.

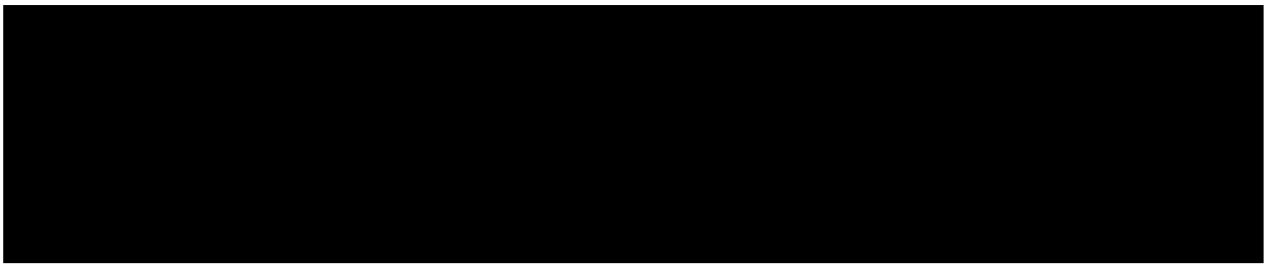
For Part-4, the geometric mean ratios and 90% confidence intervals of AUC0-inf and C_{max} will be computed for SAR442720 between fed and fasted states of tablet formulation (C1D1 to C1D15) and between the tablet (test) and capsule (reference) formulations (C1D15 to C2D1). In addition, the PK parameters 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.

4.8.2 Biomarker analyses

The biomarker analysis population is defined separately for blood-based and tumor tissue-based biomarkers. The biomarker analysis population includes all enrolled patients who receive at least one dose of any study drug and have at least one biomarker parameter from the corresponding assay sample with at least one baseline biomarker measurement.



For analysis of pharmacodynamic biomarkers, no values will be imputed for missing data.

Duplicate biomarker (ie, more than one set of data for a particular visit) is not expected. For continuous data, if duplicate data is received, the results will be averaged, and the average value will be used. The average value will be added to the analysis dataset. For non-continuous data, the results will be reviewed by the study team and a representative sample will be selected. The representative sample will be flagged in the analysis dataset.

Continuous endpoints will be summarized by descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values.

Correlations of biomarker results with measures of anti-tumor efficacy will be examined.

Graphical display will be provided for level of biomarkers at baseline and/or ratio of values to baseline at each timepoint and by cohort. Box and Whisker plots will be produced for level of biomarkers at baseline each timepoint and by cohort. Line plot will be produced for level of biomarker expression across time.

4.9 INTERIM ANALYSES

No formal interim analysis is planned.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADI:	actual dose intensity
AE:	adverse event
AESIs:	adverse events of special interest
BID:	twice a day
BIW:	twice a week
CBR:	clinical benefit rate
CI:	confidence interval
CR:	complete response
CRC:	colorectal cancer
ctDNA:	circulating tumor DNA
DLT:	dose limiting toxicities
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
IMP:	investigational medicinal product
IV:	intravenous
LLOQ:	lower limit of quantitation
MTD:	maximum tolerated dose
NCI-CTCAE:	National Cancer Institute Common Terminology for Adverse Events
NSCLC:	non-small cell lung cancer
ORR:	objective response rate
PCSA:	potentially clinically significant abnormalities
PD:	progressive disease
PDI:	planned dose intensity
PFS:	progression free survival
PK:	pharmacokinetic
PR:	partial response
RDI:	relative dose intensity
RECIST:	response evaluation criteria in solid tumors
RP2D:	recommended Phase 2 dose
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SoC:	standard of care
TEAE:	treatment-emergent adverse event
TTR:	time to response
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics, baseline characteristics, medical, surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the safety population.

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (<65, 65 to <75, ≥75)
- Gender (Male, Female)
- Race (Asian, White, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, unknown)
- Baseline height (cm)
- Baseline weight (kg)

Medical history and specific history of Pericardial Effusion will be summarized using the MedDRA version 24.1.

Disease diagnosis history will be summarized including time from initial diagnosis to first study treatment administration, cancer type, location, cancer stage, CNS involvement, extent of disease at study entry.

- If only the day-component is missing, the 15th will be used.
- If only a year is present, and it is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicates that the date is earlier.
- If only a year is present, and it is not the same as the year of the first dose of study drug, the 15th of June will be used, unless other data indicate that the date is earlier.

Prior or concomitant medications

All medications will be coded using the March 1, 2022 version of World Health Organization-Drug Dictionary (WHO-DD).

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.

- Concomitant medications are any interventions received by the participant concomitantly to any IMP during the on-treatment period/from the first administration of IMP to the last IMP intake.
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the safety population. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence in the total group. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Anticancer therapies

Prior anticancer therapies will be summarized including number of patients with at least one prior anticancer therapy, best response, number of regimens and category of regimens (0, 1, 2, >=3). In addition, patients with the prior radiation therapy and prior surgery will also be summarized.

For initial diagnosis with partial date, following rules can be applied to implement date imputation:

- If only the day-component is missing, the 15th will be used.
- If only a year is present, and it is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicates that the date is earlier.
- If only a year is present, and it is not the same as the year of the first dose of study drug, the 15th June will be used, unless other data indicate that the date is earlier.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and other safety measurements will be used for computation of baseline, the last/worst on-treatment value, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.5 INTERNATIONALLY AGREED SOC ORDER

The internationally agreed order (Guideline on summary of product characteristics, December 1999, European commission) for SOC:

1. Infections and infestations
2. Neoplasms benign and malignant (including cysts and polyps)
3. Blood and the lymphatic system disorders
4. Immune system disorders
5. Endocrine disorders
6. Metabolism and nutrition disorders
7. Psychiatric disorders
8. Nervous system disorders
9. Eye disorders
10. Ear and labyrinth disorders
11. Cardiac disorders
12. Vascular disorders
13. Respiratory, thoracic and mediastinal disorders
14. Gastrointestinal disorders
15. Hepato-biliary disorders
16. Skin and subcutaneous tissue disorders
17. Musculoskeletal, connective tissue and bone disorders
18. Renal and urinary disorders
19. Pregnancy, puerperium and perinatal conditions
20. Reproductive system and breast disorders
21. Congenital and familial/genetic disorders
22. General disorders and administration site conditions
23. Investigations
24. Injury and poisoning

25. Surgical and medical procedures
26. Social circumstances
27. Product Issues

The other terms are sorted by dictionary code order.

5.6 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA

Parameter	PCSA	Comments
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
Laboratory		
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Chloride	<80 mmol/L >115 mmol/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Blood Urea Nitrogen	≥17 mmol/L	
pH	≤4.6 ≥8	
eGFR (MDRD)	≥60 - <90 mL/min/1.73 m^2 (mild impairment) ≥30 - <60 mL/min/1.73 m^2 (moderate impairment) ≥15 - <30 mL/min/1.73 m^2 (severe impairment) <15 mL/min/1.73 m^2 (end stage renal disease)	

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