A Phase 1b/2 Open-Label Umbrella Study Of Sasanlimab Combined With Anti-Cancer Therapies Targeting Multiple Molecular Mechanisms in Participants With Non-Small Cell Lung Cancer (NSCLC)

STATISTICAL ANALYSIS PLAN – B8011011

Compounds:	PF-06801591 Encorafenib/Binimetinib Axitinib/SEA-TGT
Compound Name:	Sasanlimab BRAFTOVI (encorafenib)/MEKTOVI (binimetinib) INLYTA(axitinib)/SEA-TGT
Version:	2
Date:	24-June-2021

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B8011011 is based on the protocol amendment 3 dated 28APR2021.

Table 1. Summary of Major Changes in SAP Amendments

Version	Version Date	Summary of Changes
1	28-Aug-2020	Not applicable (N/A)
2	24-Jun-2021	The primary purpose of this amendment is to incorporate Sub-Study B into the statistical analysis plan. Additional updates were made for consistency or clarity. The term “patient” was replaced with the term “participant”. Sec 2.1.1. “Sub-Study A” – removed PD-L1 secondary objectives and endpoint from Phase 1b of Sub-Study A; changed "PD-L1 expression" secondary endpoint to "OR by PD-L1 expression" added PRO objective and endpoint. Sec 2.1.2. “Sub-Study B” – added Sub-Study B objectives, endpoints, and estimands. Sec. 2.2 “Study Design” – removed 300 mg fixed dose for sasanlimab since the dose can be sub-study dependent. Figure 1 updated. Sec. 2.2.2 “Sub-Study B Design” – added the whole new section to describe Sub-Study B design. . Sec 3.1.1 “Phase 1b” – added DLT observation period for Sub-Study B. Sec 3.1.2.2. “Sub-Study B” – added the primary endpoint of OR for Sub-Study B. 3.2.2.1. “Sub-Study A and Sub-Study B” – Definition of DR is clearified. Sec. 3.2.3 “Pharmacokinetic endpoints” – added definitions for PK parameters. Sec 3.2.4. “Immunogenicity endpoints” – added Sub-Study B treatments Sec 3.2.6. “Patient Reported Outcomes endpoints” – added the whole section. Sec 3.4.1. “Study drug, study treatment and baseline definitions” – added definitions related to Sub-Study B. Added definition of baseline for PRO and biomarker analyses. Sec 4. “Analysis sets” – added footnote with Sub-Study B per-protocol analysis set criteria. Sec 5.1.1.2. “Sub-study B” – added sample size determination for Sub-Study B. Sec 5.1.2.2. “Sub-Study B” – added decision rules for Sub-Study B. Sec 5.2. “General Methods” – added treatment groups definitions for Sub-Study B. Sec 6.1.2.2.1. “Primary analysis” – added analysis of the primary endpoint of ORR for Sub-Study B. Sec 6.2.2.3. “Duration of response” – corrected censoring condition by removing “date of randomization”. Sec 6.2.3. “Pharmacokinetic endpoints” – added PK endpoints for Sub-Study B. Sec 6.2.5. “Biomarker endpoints” – added analysis of PD-L1 biomarker for Sub-Study B. Sec 6.2.6. “Endpoints for immunogenicity data” – added Sub-Study B, clarified definitions for ADA and NAb positive/negative in Table 14. Sec 6.2.7.1. “Sub-Study A” – added analysis of PRO endpoints

		Sec 6.5.3. "Study treatment compliance and exposure" – added related to Sub-Study B treatments, analyses of exposure, dose reductions, dose interruptions, dose delays. Sec 6.6.1. "Adverse events" – added analyses related to Sub-Study B treatments. Sec 7.2. "Sub-Study B" – added a statement that the there will be no interim analysis in Sub-Study B. Sec 8. "References" – added PRO and mTPI references, rearranged order alphabetically. Appendix 2. Table "Next Dose Recommendation and the Interval probability of Target Toxicity and Overdosing at Next Dose" – added footnotes for notations. Appendix 3. "List of Abbreviations" – new abbreviations added.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B8011011. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned electronic case report form (eCRF) data as well as non-CRF data (i.e., pharmacokinetics (PK), anti-drug antibody (ADA), neutralizing antibody (NAb), and biomarker data). The primary analysis for each sub-study will include all data up to a cut-off date corresponding to 12 months after the last participant receives the first dose of study treatment. The final analysis of the data will be performed after last participant last visit (LPLV).

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1. Sub-Study A

Table 2. Sub-Study A Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
Phase 1b	**Phase 1b**
• To assess the dose limiting toxicity (DLT) rate and estimate the maximum tolerated dose (MTD) of sasanlimab in combination with encorafenib and binimetinib to recommend a phase 2 dose (RP2D) for the combination.	• DLTs during DLT-observation period.
Phase 2	**Phase 2**
• To assess the durable objective response rate (ORR) of sasanlimab in combination with encorafenib and binimetinib.	• Durable OR, defined as confirmed a complete response (CR) or partial response (PR) lasting for at least 10 months from the date of first CR or PR, as assessed by the investigator using RECIST v1.1.
Secondary:	**Secondary:**
Phase 1b	**Phase 1b**
• To assess the overall safety and tolerability of sasanlimab in combination with encorafenib and binimetinib.	• Adverse Events (AEs) graded according to the NCI-CTCAE v5.0 and changes in clinical laboratory parameters.
• To assess the anti-tumor activity of sasanlimab in combination with encorafenib and binimetinib.	• Durable OR and OR as assessed by the investigator using RECIST v1.1.
• To characterize the PK of sasanlimab, encorafenib, and binimetinib when administered in combination.	• PK parameters of sasanlimab (i.e., C_{trough}, C_{max}, T_{max}, AUC), encorafenib, binimetinib and applicable metabolites (i.e., C_{trough}) when administered in combination, as data permit.
• To evaluate the immunogenicity of sasanlimab when given in combination with encorafenib and binimetinib.	• ADA and nAb (i.e., incidence) against sasanlimab, as data permit.

Objectives	Endpoints
Secondary:	**Secondary:**
Phase 2	**Phase 2**
• To assess other measures of anti-tumor activity of sasanlimab in combination with encorafenib and binimetinib.	• Objective response (OR), duration of response (DR), time to response (TTR), progression free survival (PFS) by investigator assessment using RECIST v1.1, and overall survival (OS).
• To assess the overall safety and tolerability of sasanlimab in combination with encorafenib and binimetinib.	• AEs graded according to the NCI-CTCAE v5.0 and changes in clinical laboratory parameters.
• To characterize the PK of sasanlimab, encorafenib, and binimetinib when administered in combination	• PK parameters of sasanlimab, encorafenib, binimetinib, and applicable metabolites (i.e., C_{trough}) when administered in combination, as data permit.
• To evaluate the immunogenicity of sasanlimab when given in combination with encorafenib and binimetinib.	• ADA and nAb (i.e., incidence) against sasanlimab, as data permit.
• To assess the correlation between anti-tumor activity and PD-L1 expression in baseline tumor biopsies.	• OR by PD-L1 expression in baseline tumor samples.
• To assess the effects of sasanlimab, encorafenib, and binimetinib on patient-reported health-related quality of life.	• Health-related quality of life as measured by EORTC QLQ-C30/LC13
Tertiary/Exploratory:	**Tertiary/Exploratory:**
Phase 1b and Phase 2	**Phase 1b and Phase 2**
• To understand the relationship between the therapeutic intervention(s) being studied and the biology of the participant's disease.	• Measurements of biomarkers, consisting of DNA, RNA, protein, metabolites or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment or at end-of-study.
Phase 2	**Phase 2**
• To assess additional measure of anti-tumor activity of sasanlimab in combination with encorafenib and binimetinib.	• Depth of response by investigator assessment using RECIST v1.1.

Primary Estimand(s)

Phase 1b:

Primary Estimand (DLT): DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period (Cycle 1 – first 28 days of study treatment) in Phase 1b.

- Variable: Occurrence of DLTs.
- Analysis population: DLT-evaluable participants defined as participants who receive at least 1 dose of the combination study treatment in Phase 1b and either experience DLT during the DLT-evaluation period or complete the DLT-evaluation

period without DLT. Participants without DLTs who receive less than 75% of the planned dose of each study drug in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.
- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants in the DLT-evaluation period.

Phase 2:

Primary Estimand (Durable OR): the treatment effect of sasanlimab + encorafenib + binimetinib assessed by the Durable ORR, based on Investigator assessment per RECIST v1.1, in the analysis population.

- Variable: Durable objective response defined as confirmed CR or PR according to RECIST v1.1 based on investigator assessment, lasting for at least 10 months from the date of first CR or PR until the date of the first documentation of PD, death, or start of new anticancer therapy. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.
- Analysis population: all participants who received at least 1 dose of study drug without regard to tolerability or duration of treatment.
- Population-level summary measure: Durable ORR defined as the proportion of participants in the analysis population with durable OR and 2-sided 95% CI for durable ORR using the Clopper-Pearson method. Participants who do not have a postbaseline tumor assessment due to early progression of disease, who receive anticancer therapies other than the study treatments prior to reaching a CR or PR for 10 months, or who die, have PD, or stop tumor assessments for any reason prior to reaching a CR or PR for 10 months will be counted as non-responders in the assessment of durable OR. Each participant will have a durable objective response status (0: no durable OR; 1: durable OR).

2.1.2. Sub-Study B

Table 3. Sub-Study B Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
Phase 1b	**Phase 1b**
• To assess the DLT rate and estimate the MTD of sasanlimab in combination with axitinib and SEA-TGT to determine the RP2D for the combination.	• DLTs during the DLT-observation period.
Phase 2	**Phase 2**
• To assess the ORR of sasanlimab in combination with axitinib and SEA-TGT.	• OR, defined as confirmed CR or PR, as assessed by the investigator using RECIST v1.1.
Secondary:	**Secondary:**
Phase 1b	**Phase 1b**

Objectives	Endpoints
• To assess the overall safety and tolerability of the combined investigational products.	• AEs graded according to the NCI-CTCAE v5.0 and changes in clinical laboratory test parameters.
• To assess the anti-tumor activity of the combined investigational products.	• OR, DR, TTR, PFS by investigator assessment using RECIST v1.1.
• To characterize the PK of the investigational products.	• PK parameters (Cmax, Ctrough) of sasanlimab, axitinib, and SEA-TGT, as data permit.
• To evaluate the immunogenicity of sasanlimab.	• ADA (i.e., incidence) against sasanlimab, as data permit.
• To evaluate the immunogenicity of SEA-TGT.	• ADA (i.e., incidence) against SEA-TGT, as data permit.
Phase 2	**Phase 2**
• To assess other measures of anti-tumor activity of the combined investigational products.	• DR, TTR, PFS by investigator assessment using RECIST v1.1, and OS.
• To assess the overall safety and tolerability of the combined investigational products.	• AEs graded according to the NCI-CTCAE v5.0 and changes in clinical laboratory test parameters.
• To characterize the PK of the investigational products.	• PK parameters (Cmax, Ctrough) of sasanlimab, axitinib, and SEA-TGT, as data permit.
• To evaluate the immunogenicity of sasanlimab.	• ADA against sasanlimab, as data permit.
• To evaluate the immunogenicity of SEA-TGT.	• ADA against SEA-TGT, as data permit.
• To assess the association between anti-tumor activity and PD-L1 expression.	• OR by PD-L1 expression in available tumor tissue (archival or de novo, primary or metastatic).
Exploratory	**Exploratory**
Phase 1b	**Phase 1b**
• To understand the relationship between the therapeutic interventions being studied and the biology of the participant's NSCLC. •	• Biomarkers, consisting of DNA, RNA, protein, metabolites or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment or at end-of-study.
Phase 2	**Phase 2**
• To understand the relationship between the therapeutic interventions being studied and the biology of the participant's NSCLC.	• Biomarkers, consisting of DNA, RNA, protein, metabolites or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment or at end-of-study.

Primary Estimand(s)

Phase 1b:

Primary Estimand (DLT): DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period (Cycle 1 – first 21 days of study treatment) in Phase 1b.

Variable: Occurrence of DLTs.

Analysis population: DLT-evaluable participants defined as participants who receive at least 1 dose of the combination study treatment in Phase 1b and either experience DLT during the DLT-evaluation period or complete the DLT-evaluation period without DLT. Participants

without DLTs who receive less than 75% of the planned dose of each study intervention in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.

Population-level summary measure: DLT rate defined as the number of DLT evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants in the DLT-evaluation period.

Phase 2:

Primary Estimand (OR): the treatment effect of sasanlimab + axitinib + SEA-TGT assessed by the ORR, based on Investigator assessment per RECIST v1.1, in the analysis population.

- Variable: Objective response defined as confirmed CR or PR according to RECIST v1.1 based on investigator assessment. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

- Analysis population: all participants who received at least 1 dose of study intervention without regard to tolerability or duration of treatment.

- Population-level summary measure: ORR is defined as the proportion of participants in the analysis population with an OR and 2-sided 95% CI for ORR using the Clopper-Pearson method. Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, or have PD, or stop tumor assessments for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: no OR; 1: OR).

2.2. Study Design

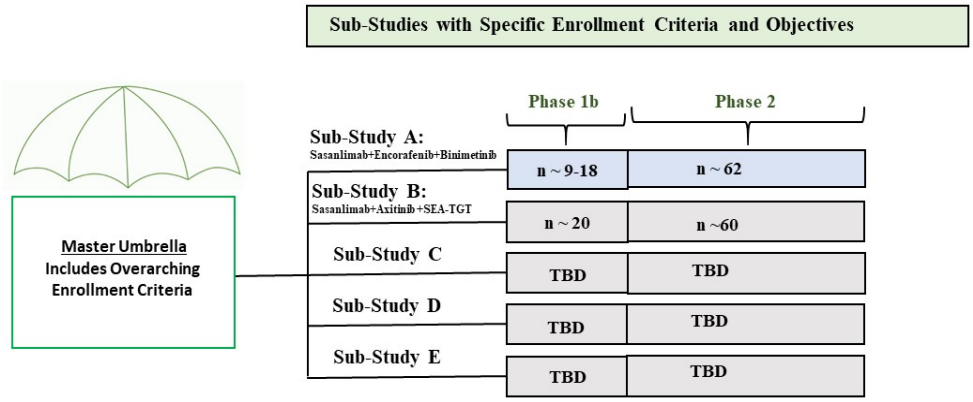
This is a prospective, open-label, multi-center, parallel group, Phase 1b/2 umbrella study to evaluate safety, efficacy, pharmacokinetics, and/or pharmacodynamics of sasanlimab in combination with targeted agents that increase anti-tumor immunity and activity in adult participants with locally advanced or metastatic NSCLC. Each sub-study may be conducted in parallel, as new agents are included to begin a sub-study within the framework of the master protocol. Each sub-study will specify the treatment setting. Participants will receive study interventions until permanent treatment discontinuation criteria are met.

The combination arms will be assessed individually in 2 parts:

1. A Phase 1b part to evaluate safety of the combination and select an RP2D dose level for the combination.

2. A Phase 2 part to evaluate the activity and further evaluate safety of the RP2D from the Phase 1b part in pre-specified participant populations.

Figure 1. Study Design Schema



2.2.1. Sub-study A Design

Phase 1b

The sasanlimab dose will remain fixed for all dosing cohorts in the Phase 1b part of Sub-Study A.

Beginning with the starting dose level, cohorts of 3-6 participants will be enrolled, treated, and monitored during the 28-day DLT evaluation period (Cycle 1). Participants without DLTs who receive less than 75% of the planned dose of each study drug in the combinations in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. A minimum of 3 DLT-evaluable participants will be required; additional participants will be enrolled in the specific enrollment cohort to replace participants who are not considered DLT-evaluable, where required. When all DLT-evaluable participants treated in a given enrollment cohort have completed the DLT observation period or experienced a DLT, whichever occurs first, the posterior distribution for the risk of DLT for new participants at different dose levels for the combination of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the intervals shown below:

- Underdosing: [0, 0.16);
- Target toxicity: [0.16, 0.33);
- Excessive toxicity: [0.33, 1].

In addition to accumulating safety data and observed DLTs, decisions on further participant enrollment and dose level selection will be guided by the escalation with overdose control (EWOC) criterion. A combination dose may only be used for newly enrolled participants if the risk of excessive toxicity at that combination dose is less than 25% (0.25). Refer to Appendix 2 for further details of the BLRM.

An RP2D below the MTD, or highest safe dose tested, may be determined based on other safety, clinical activity, PK, and pharmacodynamic data. Before expanding into Phase 2, safety will be confirmed in at least 9 DLT-evaluable participants treated at the RP2D.

Table 4. Sub-Study A Combination: Sasanlimab + Encorafenib + Binimetinib – Available Dose Levels

Dose Level	Sasanlimab	Encorafenib	Binimetinib
1	300 mg SC Q4W	450 mg QD	45 mg BID
0 (starting dose)	300 mg SC Q4W	300 mg QD	45 mg BID
-1	300 mg SC Q4W	300 mg QD	30 mg BID

DLT period = 1 cycle. The treatment cycle is 28 days.
BLRM dose escalation schema will be used for the dose-finding phase of the study.

Phase 2 Design:

Phase 2 Sub-Study A will enroll approximately 62 participants with $BRAF^{V600}$-mutated NSCLC and will evaluate the activity and safety of sasanlimab + encorafenib + binimetinib.

2.2.2. Sub-study B Design

Phase 1b

Phase 1b will enroll participants in any line therapy for advanced NSCLC with no restrictions on the types of previous therapies, and who have any PD-L1 expression status. First, the safety of the sasanlimab and axitinib combination will be confirmed. Up to 2 dose levels of axitinib given in combination with sasanlimab CCI will be investigated (Table 5). The decision to de-escalate axitinib (from 5 mg BID to 3 mg BID) will be based on mTPI decision criteria based on the number of DLT evaluable participants and number of DLTs in those participants.

Initially 3-4 participants will be treated with sasanlimab CCI + axitinib 5 mg BID and monitored during the 21-day DLT evaluation period (Cycle 1). If the mTPI decision criteria allow escalation, then the triplet cohort may be opened. Otherwise, the doublet cohort can be expanded with an additional 3 participants enrolled or de-escalated to the lower dose (3 mg BID) per the mTPI decision criteria.

Table 5. Sub-Study B Phase 1b, Doublet Cohorts Dose Levels

Dose Level	Sasanlimab	Axitinib

0 (Starting Dose)	CCI		5 mg BID
-1	CCI		3 mg BID

DLT period = 1 cycle of 21 days.
mTPI dose finding schema will be used for dose finding.

After the safety of the doublet is confirmed, the triplet combination may be opened. Up to three dose levels of SEA-TGT may be investigated (Table 6) and initially 3-4 participants will be treated and monitored at the starting dose level. The enrollment of subsequent participants (dose escalation or de-escalation cohorts) will be guided by mTPI design. At least 6 participants will be treated at the RP2D of the triplet combination before proceeding to Phase 2.

Table 6. Sub-Study B, Phase 1b, Triplet Cohorts Dose Levels

Dose Level	Sasanlimab	Axitinib*	SEA-TGT**
1	CCI	3 or 5 mg BID	Single-agent RP2D IV Q3W
0 (Starting Dose)	CCI	3 or 5 mg BID	Single-agent RP2D -1 IV Q3W
-1	CCI	3 or 5 mg BID	Single-agent RP2D -2 IV Q3W

DLT period = 1 cycle of 21 days.
mTPI dose finding schema will be used for dose finding.
*Axitinib dose will be determined by the doublet cohorts and will be fixed in the triplet cohorts.
**Final dose pending ongoing first-in-human monotherapy study exploring 0.01, 0.1, 0.3, 1, 3, and 10 mg/kg (SGNTGT-001).

A minimum of 3 DLT-evaluable participants will be required in each cohort; additional participants will be enrolled in the specific enrollment cohort to replace participants who are not considered DLT-evaluable, where required. When all DLT-evaluable participants treated in a given enrollment cohort have completed the DLT observation period or experienced a DLT, whichever occurs first, the posterior probabilities for the risk of DLT for new participants at different dose levels for the combination of interest will be evaluated. If the toxicity rate of the currently used dose level is far smaller than the target probability of toxicity (pT) of 0.30, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. The mTPI dose de-escalation/escalation recommendation will be based on the estimated toxicity rate and 3 intervals (underdosing, target toxicity, and excessive toxicity) as shown below:

- If current dose is in the underdosing [0, 0.25) toxicity interval: escalate to next higher dose;
- If current dose is in the target toxicity [0.25, 0.35) toxicity interval: stay at current dose;
- If current dose is in the excessive toxicity or overdosing [0.35, 1] toxicity interval: de-escalate to a lower dose

The number of participants to be enrolled in Phase 1b will depend upon the observed safety profile, which will determine the number of participants at each dose level and the number of dose levels explored.

It is anticipated that up to approximately 20 total participants will be enrolled in Phase 1b starting with Dose Level 0 of the doublet cohorts and including the triplet cohorts.

An RP2D below the MTD, or highest safe dose tested, may be determined based on other safety, clinical activity, PK, and pharmacodynamic data.

Cumulative DLT data will continue to be evaluated using the mTPI design in the Phase 2 part. Should emerging data indicate that the dose level tested in the Phase 2 expansion cohort is more toxic than previously estimated (≥ 35% DLT rate), the next lower dose level may be explored, and may be declared as the RP2D for the triplet combination.

Phase 2 Design:

Once the RP2D of the triplet is defined, the Phase 2 part of the study may be initiated. Participants will be allocated to 1 of 3 treatment arms based on lines of prior therapy and PD-L1 TPS. For participants with previously untreated NSCLC, competitor data for PDx/TIGIT doublet combinations suggest that clinical activity may be enriched in the subgroup of participants with PD-L1 TPS ≥50% as compared to those with PD-L1 TPS 1-49%. Therefore, participants will be enrolled into 2 separate treatment arms based on PD-L1 expression to allow for estimation of clinical activity in each subgroup:

- Treatment Arm B1 (n=20): treatment-naïve participants with low PD-L1 (levels 1-49%);
- Treatment Arm B2 (n=20): treatment-naïve participants with high PD-L1 (levels ≥50%).

Given the existing data and high unmet need, a 3rd group of participants who have received prior checkpoint treatment is planned:

- Treatment Arm B3 (n=20): participants whose disease has progressed on prior PD-1/PD-L1 therapy and who have PD-L1 TPS ≥ 1%.

Phase 2 will enroll a total of approximately 60 participants and will evaluate the anti-tumor activity and further evaluate the safety of the triplet combination of sasanlimab + axitinib + SEA-TGT.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Endpoints specific to a Sub-Study are indicated.

3.1. Primary Endpoint(s)

3.1.1. Phase 1b

DLT during the DLT-observation period is the primary safety endpoint of Phase 1b for the combination evaluated.

- For Sub-Study A the DLT-observation period is the first 28 days after and including the date of first dose (i.e. Cycle 1 Day 1 through Cycle 1 Day 28).

- For Sub-Study B the DLT-observation period is the first 21 days after and including the date of first dose (i.e., Cycle 1 Day 1 through Cycle 1 Day 21).

3.1.2. Phase 2

3.1.2.1. Sub-Study A

- Durable OR is defined as a complete response (CR) or partial response (PR) according to RECIST v1.1 from the date of first dose of study treatment until the date of the first documentation of progressive disease (PD) and lasting for at least 10 months (298 days) from the date of first documentation of the CR or PR until progression or death. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

  Participants are considered to have had a durable OR if they had response lasting for ≥ 10 months (298 days). Each participant will have a durable objective response status (0: no durable OR; 1: durable OR).

3.1.2.2. Sub-Study B

- OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the date of first study treatment until the date of the first documentation of progressive disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

3.2. Secondary Endpoints

3.2.1. Safety endpoints

- AEs graded according to the NCI-CTCAE v5.0 and changes in clinical laboratory parameters.

  AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA)

3.2.2. Efficacy endpoints

3.2.2.1. Sub-Study A and Sub-Study B

Durable OR (for Phase 1b Sub-Study A only refer to Section 3.1.2.1), OR (Phase 1b and Phase 2), TTR (Phase 2), DR (Phase 2), and PFS (Phase 2) will be summarized based on investigator assessment using RECIST v1.1. OS will be summarized for Phase 2.

- OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the date of first study treatment until the date of the first documentation of progressive disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

- TTR is defined for participants with OR, as the time from the date of first dose of study treatment to the date of first documentation of objective response (CR or PR) which is subsequently confirmed.

- DR is defined for participants with confirmed OR, as the time from the the date of first documentation of OR to the date of the first documentation of PD or to death due to any cause, whichever occurs first.

- PFS is defined as the time from the date of first dose of study treatment to the date of first documentation of PD or death due to any cause, whichever occurs first.

- OS is defined as the time from the date of first dose of study treatment to the date of death due to any cause.

3.2.3. Pharmacokinetic endpoints

- PK parameters of sasanlimab, encorafenib, binimetinib (Sub-Study A), sasanlimab, axitinib, SEA-TGT (Sub-Study B), and applicable metabolites, as data permit.

- PK parameters for sasanlimab include AUC, Cmax, Tmax and Ctrough (Sub-Study A and B).

- PK parameters of interest for encorafenib, binimetinib (Sub-Study A only) include Ctrough

- PK parameters of interest for axitinib (Sub-Study B only) include Cmax and Ctrough

- PK parameters of interest for SEA-TGT (Sub-Study B only) include AUC, Cmax, and Ctrough.

Table 3. Definitions for PK Parameters to be Determined as Data Permit

Parameter	Definition	Method of Determination
AUCsd,τ AUCss,τ	Area under the plasma concentration-time profile from time zero to the next dose (after single dose and at steady state)	Linear/Log trapezoidal method
Cmax	Maximum observed plasma concentration	Observed directly from data
Tmax	Time for Cmax	Observed directly from data as time of first occurrence
t½a	Terminal half-life	Log(2)/kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
Ctrough	Pre-dose concentration during multiple dosing	Observed directly from data

CL/Fa	Apparent clearance	Dose / AUCτ for steady state
Vz/Fa	Apparent volume of distribution	Dose / (AUCτ ·kel) for steady state
AUCsd,τ (dn) AUCss,τ (dn)	Dose normalized AUC	AUC / Dose
Cmax(dn)	Dose normalized Cmax	Cmax / Dose

3.2.4. Immunogenicity endpoints

- ADA and nAb (i.e., incidence) against sasanlimab (Sub-Study A), sasanlimab and SEA-TGT (Sub-Study B), as data permit

3.2.5. Biomarker endpoints

- PD-L1 expression in baseline tumor samples

Table 7. Biomarker Definition and Determination

Parameter	Definition	Method of Determination
PD-L1 expression	The percent of counted cells scored as PD-L1+ and qualitative assessment of PD-L1 staining on tumor and immune cells as defined by cell morphology in regions of interest	Pathologist, assisted by image analysis

3.2.6. Patient Reported Outcomes endpoints

- Health-related quality of life as measured by EORTC QLQ-C30/LC13

PROs endpoints (for Phase 2 Sub-Study A only) will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and its corresponding module for lung cancer (EORTC QLQ-LC13) [4].

The EORTC QLQ-C30 consists of 30 questions, which can be grouped into 5 functional scales (physical, role, cognitive, emotional, and social); a global health status/global quality of life scale; 3 symptom scales (fatigue, pain, nausea and vomiting); and 6 single items that assess additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea); and financial impact. All scales and single item measures range in score from 0 to 100. Higher scores on the global health status/quality of life scale represent higher health status/quality of life. Higher scores on the functional scales represent higher levels of functioning. Higher scores on the symptom scales/items represent a greater presence of symptoms.

The EORTC QLQ-LC13 is the lung cancer specific module of the EORTC Quality of Life Questionnaire. The EORTC QLQ-LC13 consists of 13 questions and includes 1 multi-item scale and 9 single items assessing symptoms (dyspnea, cough, haemoptysis, and site specific pain), side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication use. Similar to the EORTC QLQ-C30, higher scores are reflective of a greater presence of symptoms.

3.3. Exploratory Endpoints

3.3.1. Sub-study A and Sub-Study B

- Measurements of biomarkers, consisting of DNA, RNA, protein, metabolites or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment or at end-of-study.

- Depth of response by investigator assessment using RECIST v1.1 (Sub-Study A).

  Depth of response is defined as a reduction in tumor burden (the sum of the diameters of target lesions). Depth of response will be summarized as a Deep Response, which is a confirmed response per RECIST v1.1 with a depth of response of at least 50%.

  Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anti-cancer therapies other than the study treatments prior to reaching a depth of response of at least 50% or who die, have PD, or stop tumor assessments for any reason prior to reaching a depth of response of ≥50% will be counted as not having a Deep Response. Each participant will have a deep response status (0: depth of response <50% OR; 1: depth of response ≥50%).

3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

In this study, '**study drug**' refers to sasanlimab or encorafenib or binimetinib for Sub-Study A, sasanlimab or axitinib or SEA-TGT for Sub-Study B, and '**study treatment**' (or '**treatment group**') refers to:

- Phase 1b Sub-Study A Dose Level 0: sasanlimab 300mg + encorafenib 300mg + binimetinib 45mg

- Phase 1b Sub-Study A Dose Level 1: sasanlimab 300mg + encorafenib 450mg + binimetinib 45mg

- Phase 1b Sub-Study A Dose Level -1: (sasanlimab 300mg + encorafenib 300mg + binimetinib 30mg

- Phase 2 Sub-Study A: To be determined from Phase 1b

- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 5 mg BID

- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 3 mg BID

- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 5 mg BID + SEA- TGT DL0

- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 5 mg BID + SEA- TGT DL1

- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 5 mg BID + SEA- TGT DL-1

- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 3 mg BID + SEA- TGT DL0
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 3 mg BID + SEA- TGT DL1
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 3 mg BID + SEA- TGT DL-1
- Phase 2 Sub-Study B: To be determined from Phase 1b

Phase 2 Sub-Study B participants will be assigned in the following 3 study arms:

  - Arm B1: Participants who report (i) no prior advanced or metastatic therapy and (ii) locally assessed PD-L1 TPS≥50%
  - Arm B2: Participants who report (i) no prior advanced or metastatic therapy and (ii) locally assessed PD-L1 TPS≥1% and TPS<50%
  - Arm B2: Participants who report (i) prior advanced or metastatic therapy and (ii) locally assessed PD-L1 TPS≥1%

Start and end dates of study treatment:

The date/time of first dose of study treatment in a combination group is the earliest date/time of the first non-zero dose date/time for the study drugs in the combination.

The date/time of last dose of study treatment in a combination group is the latest date/time of the last non-zero dose date/time for the study drugs in the combination.

Definition of baseline:

Definition of baseline for efficacy and PRO analyses and for safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety and efficacy analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Participants who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit). Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. Triplicate ECGs are collected in the study and the baseline for each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on RR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

Definition of baseline for immunogenicity analyses

The last available assessment prior to the start of treatment with sasanlimab is defined as 'baseline' result or 'baseline' assessment. If an assessment is planned to be performed prior to the first dose of sasanlimab in the protocol and the assessment is performed on the same day as the first dose of sasanlimab, it will be assumed that it was performed prior to sasanlimab administration, if assessment time point is not collected or is missing.

Definition of baseline for biomarker analyses

The last assessment prior to first dose of study treatment will serve as the baseline assessment for biomarker analyses. For biomarkers that are planned to be assessed on Cycle 1 Day 1, it will be assumed that the assessment was performed prior to study treatment administration, if the assessment time point is not collected or is missing.

3.4.2. Baseline characteristics

Baseline characteristics (including demographics, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.5. Safety Endpoints

3.5.1. Adverse events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

Adverse Events of Special Interest (AESIs)

AESIs are immune-related adverse events (irAE). The criteria for classification of an AE as an irAE are described in Appendix 1.

4. ANALYSIS SETS

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only participants who signed informed consent will be included in the analysis sets below.

Participant Analysis Set	Description
Full analysis set (FAS)	The full analysis set includes all participants who receive at least 1 dose of study drug. Participants will be classified according to the treatment actually received.
Safety analysis set	The safety analysis set includes all participants who receive at least 1 dose of study drug. Participants will be classified according to the study treatment actually received. In this non-randomized study the full analysis set and safety analysis set are identical.
Per-protocol analysis set*	The per-protocol analysis set is a subset of the full analysis set and will not include participants who do not meet criteria that could impact the key objectives of the study*. The per protocol analysis set will be used for sensitivity analyses of the primary efficacy endpoint(s).
DLT-Evaluable analysis set	The DLT-evaluable analysis set includes all participants who receive at least 1 dose of study treatment in Phase 1b and either experience DLT during the DLT-observation period or complete the DLT-observation period without DLT. Participants without DLTs receive less than 75% of the planned dose of each study drug in during the DLT observation period for reasons other than treatment-related toxicity are not evaluable for DLT.
Biomarker analysis set	The biomarker analysis set is a subset of the safety analysis set and includes all participants with at least 1 biomarker evaluated pre-dose.
Pharmacodynamic analysis set	The pharmacodynamic analysis set is a subset of the safety analysis set and includes participants with at least 1 biomarker evaluated pre- and post-dose.
Immunogenicity analysis set	The immunogenicity analysis set is a subset of the safety analysis set and includes participants who have at least 1 analyzed sasanlimab ADA/NAb sample.
PK analysis set	The PK concentration analysis set is a subset of the safety analysis set and will include participants who have at least 1 concentration of any measured analyte related to study drug (i.e., sasanlimab, etc). The PK parameter analysis set is a subset of the safety analysis set and will include participants who have at least 1 of the PK parameters of interest for the measured analytes related to the study drug (i.e., sasanlimab, etc).

*For Sub-Study A criteria: NSCLC with BRAFV600 mutations
*For Sub-Study B criteria: NSCLC with TPS≥1%

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and sample size determination

5.1.1.1. Sub-study A

For Phase 1b, the number of participants to be enrolled in Sub-Study A will depend upon the observed safety profile, which will determine the number of participants at each dose level and the number of dose levels explored. Approximately 9-18 participants will be enrolled in the Phase 1b part for each sub-study.

Beginning with the starting dose level, cohorts of 3-6 participants will be enrolled, treated, and monitored during the 28-day DLT evaluation period (Cycle 1). Participants without DLTs who receive less than 75% of the planned dose of the study intervention in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. A minimum of 3 DLT-evaluable participants will be required; additional participants will be enrolled in the specific enrollment cohort to replace participants who are not considered DLT-evaluable, where required. When all DLT-evaluable participants treated in a given enrollment cohort have completed the DLT observation period or experienced a DLT, whichever occurs first, the posterior distribution for the risk of DLT for new participants at different dose levels for the combination of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the intervals shown below:

- Underdosing: [0, 0.16);
- Target toxicity: [0.16, 0.33);
- Excessive toxicity: [0.33, 1].

In addition to accumulating safety data and observed DLTs, decisions on further participant enrollment and dose level selection will be guided by the escalation with overdose control (EWOC) criterion. A combination dose may only be used for newly enrolled participants if the risk of excessive toxicity at that combination dose is less than 25% (0.25). Refer to Appendix 2 for further details of the BLRM.

An RP2D below the MTD, or highest safe dose tested, may be determined based on other safety, clinical activity, PK, and pharmacodynamic data. Before expanding into Phase 2, safety will be confirmed in at least 9 DLT-evaluable participants treated at the RP2D for each combination.

For Phase 2, approximately 62 participants will be enrolled in the Phase 2 part of Sub-Study A.

Phase 2 will test the null hypothesis that the durable ORR does not exceed 35% (H_0: durable ORR $\leq$35%). The null hypothesis will be tested against the alternative (H_1: durable ORR >35%) at one-sided level of significance $\alpha = 0.025$ using the binomial distribution.

Sixty-two (62) participants will provide at least 90% power to reject the null hypothesis if the true durable objective response rate is at least 55% (durable ORR ≥55%).

5.1.1.2. Sub-study B

Approximately 20 participants will be enrolled in the Phase 1b dose finding part to evaluate DLTs during the first cycle of treatment in order to confirm the safety of the doublet and triplet combinations and identify the RP2D. However, the total number of participants will depend on the observed safety profile, which will determine the number of participants at each dose level and the number of dose levels explored. Beginning with the first dose level, participants will be enrolled, treated, and monitored in cohorts of 3-4 participants during the 21-day DLT evaluation period (Cycle 1). At least 6 participants will be treated at the RP2D of the triplet combination before proceeding to Phase 2.

Phase 1b will use the mTPI dose finding design with the target toxicity rate of 0.30 with target toxicity interval of (0.25, 0.35).

For Phase 2, approximately 60 participants (20 each in Arms B1, B2 and B3) in total will be enrolled in the Phase 2 part of Sub-Study B.

The primary goal of Phase 2 is to estimate the ORR with standard error ≤0.11. Twenty participants per each treatment arm will provide the specified precision of ORR estimates.

5.1.2. Decision rules

5.1.2.1. Sub-Study A

Phase 1:

The dosing decision and estimation of the MTD of the triplet combination will be guided by the estimation of the probability of DLT in Cycle 1. However, other evidence such as safety data beyond DLT, clinical activity, PK, and PD data will play an important role in the final decision. A RP2D below the MTD may be determined based on these considerations.

Bayesian adaptive approach

The dose finding in the Phase 1b of the study will be guided by a Bayesian analysis of Cycle 1 DLTs in DLT-evaluable participants.[5]

Triplet combination model

For the triplet combination of encorafenib, binimetinib, and sasanlimab, the Bayesian mode[8] consists of seven parts, representing:

1. Single-agent encorafenib toxicity;

2. Single-agent binimetinib toxicity;

3. Single-agent sasanlimab toxicity;

4. Interaction between encorafenib and binimetinib;

5. Interaction between binimetinib and sasanlimab;

6. Interaction between encorafenib and sasanlimab;

7. Triple interaction among encorafenib, binimetinib, and sasanlimab.

Single-agent toxicities are modelled using logistic regression for the probability of a participant experiencing a DLT against log-dose. The odds of a DLT are then calculated under no interaction for the two/three single-agent toxicities, and interaction is accounted for by adjusting these odds with an additional model parameter (odds multiplier). Details of the model are given in Appendix 2.

Assessment of participant risk

After each dosing cohort of participants completes the DLT evaluation period, the posterior distribution for the risk of DLT for different dose combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

- Underdosing: [0, 0.16);
- Target toxicity: [0.16, 0.33);
- Excessive toxicity: [0.33, 1].

The EWOC principle

Dosing decisions are guided by the EWOC principle[1]. A combination dose may only be used for the next dosing cohort of participants if the risk of excessive toxicity ([0.33, 1]) at that combination dose is less than 0.25.

Prior distributions

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data[1,8,9] .
MAP priors are derived using Bayesian hierarchical models, which take into account possible differences between the studies.

A full description of the application of the MAP approach to derive the prior distributions of the single-agent model parameters is given in Appendix 2.

The prior distribution for the interaction parameters (doublet and triplet combinations) were based on the prior understanding of possible drug safety interactions. This prior allows for the possibility of either synergistic or antagonistic interaction, and is fully described in Appendix 2).

It is estimated that up to 18 participants will be enrolled and assigned to treatment with the triplet combination which will include at least 6 participants treated at the MTD level and at least 9 participants at the RP2D. The actual number of participants will depend on the number of DLT events and dose levels tested

Phase 2:

At the end of Phase 2:

- If there are ≤29 objective durable responders of 62 participants in the Phase 2 part, then it will be declared that the null hypothesis cannot be rejected.

- If there are ≥30 objective durable responders of 62 participants in the Phase 2 part, then the null hypothesis will be rejected.

5.1.2.2. Sub-Study B

A safe dose will be determined using the adaptive mTPI design. The mTPI design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target probability (pT) rate (pT=0.30). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend deescalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model. As shown by Ji and Wang[5], mTPI design is more efficient and safer than the 3+3 design. They considered 42 scenarios to cover a wide range of practical dose-response shapes, and concluded that the 3 + 3 design was more likely to treat participants at toxic doses above the MTD and less likely to identify the true MTD than the mTPI design. For example, the 3 + 3 design exhibited a lower overall toxicity percentage than the mTPI design in only 1 of 42 scenarios.

Decision rules are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and overdosing in terms of toxicity (Table 8). Specifically, the underdosing interval is defined as [0, pT-e1), the overdosing interval (pT+e2, 1], and the proper-dosing interval [pT- e1, pT+ e2), where e1 and e2 are small fractions. Based on the projected safety profile, e1 is selected as 0.05, and e2 is selected as 0.05. Therefore, the target interval for the DLT rate is [0.25, 0.35). The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given a dosing interval and a probability distribution, the UPM of that dosing interval is defined as the probability of a participant belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future participants. For example, if the underdosing interval has the largest UPM, the decision will be to escalate, and the next 3-4 participants will be treated at the next higher dose level. Simulations have demonstrated that

the decision based on UPM is optimal in that it minimizes a posterior expected loss (i.e., minimizes the chance of making a wrong dosing decision).

Table 8. Dose Finding Rules

		Number of Participants Treated at Current Dose															
	r\n	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Number of DLTs	0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	1	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E
	2	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E
	3	DU	DU	D	S	S	S	S	S	S	S	S	S	S	E	E	E
	4		DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S
	5			DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
	6				DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S
	7					DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S
	8						DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S
	9							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
	10								DU	DU	DU	DU	DU	DU	DU	DU	DU
	11									DU	DU	DU	DU	DU	DU	DU	DU
	12										DU	DU	DU	DU	DU	DU	DU
	13											DU	DU	DU	DU	DU	DU
	14												DU	DU	DU	DU	DU
	15													DU	DU	DU	DU
	16														DU	DU	DU
	17															DU	DU
	18																DU

E = Escalate to the next higher dose level
S = Stay at the current dose level
D = De-escalate to the next lower dose level
DU = The current dose level is unacceptably toxic and should be eliminated from further dose finding
DLTs = Dose Limiting Toxicities; Targeted DLT rate=30%

Select escalation/de-escalation algorithms for total number of participants treated at the current dose level (current and previous cohorts):

For example based on Table 8, with 6 participants treated at current dose level

- 0-1 DLT: escalate
- 2-3 DLTs: remain at the same dose
- 4-6 DLTs: de-escalate and consider current dose as intolerable

5.2. General Methods

As described in Section 3.4, in this study '**treatment group'** refers to:

- Phase 1b Sub-Study A Dose Level 0: sasanlimab 300mg + encorafenib 300mg + binimetinib 45mg

- Phase 1b Sub-Study A Dose Level 1: sasanlimab 300mg + encorafenib 450mg + binimetinib 45mg
- Phase 1b Sub-Study A Dose Level -1: sasanlimab 300mg + encorafenib 300mg + binimetinib 30mg
- Phase 2 Sub-Study A: To be determined from Phase 1b
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 5 mg BID
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 3 mg BID
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 5 mg BID + SEA- TGT DL0
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 5 mg BID + SEA- TGT DL1
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 5 mg BID + SEA- TGT DL-1
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 3 mg BID + SEA- TGT DL0
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 3 mg BID + SEA- TGT DL1
- Phase 1b Sub-Study B: sasanlimab CCI + axitinib 3 mg BID + SEA- TGT DL-1
- Phase 2 Sub-Study B: To be determined from Phase 1b

The following will be provided by sub-study and corresponding treatment groups.

Baseline characteristics, disposition, and efficacy data will be summarized based on the FAS by sub-study and treatment group.

DLTs will be summarized based on the DLT-evaluable set by sub-study and treatment group including data from Phase 1b only.

Other safety data, exposure data, concomitant medications and non-drug treatments will be summarized based on the safety analysis set by sub-study and treatment group.

PK data will be summarized based on the PK analysis set by sub-study and treatment group.

Biomarker data will be summarized based on the biomarker analysis set by sub-study and treatment group.

Immunogenicity data will be summarized based on the immunogenicity analysis set by sub-study and by treatment group, if data permit.

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The ‘center’ factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants treated at each center.

5.2.3. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics i.e., number of non-missing values and number of missing values [i.e., n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of participants still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (e.g., adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (e.g., baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of start of new anti-cancer drug therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the ‘Follow-up Cancer Therapy’ or ‘Concomitant Medication” eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using only data from the ‘Follow-up Cancer Therapy’ eCRF pages.

5.2.6. Definition of start of new anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 6.1.2 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the first dose of study treatment amongst the following:

- Start date of anti-cancer drug therapy recorded in the ‘Follow-up Cancer Therapy’ eCRF pages

- Start date of radiation therapy recorded in 'Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'
- Surgery date recorded in 'On Study Follow up Cancer Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Radiation Therapy', 'On Study Follow up Cancer Surgery' eCRF pages.

5.2.7. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. E.g., 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits (if such analyses are performed).

5.2.10. Adequate baseline tumor assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including the date of first dose of study treatment.
- All documented lesions must have non-missing assessments (i.e., non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

5.2.11. Adequate post-baseline tumor assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined (see Section 6.2.2.1). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg when they cannot be calculated, should be presented as 'ND' or 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1.1. Pharmacokinetic concentrations

Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (i.e., not done) or NS (i.e., no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

5.3.1.2. Pharmacokinetic parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses. If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (i.e., not calculated). NC values will not be generated beyond the day that a participant discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (i.e., analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Handling of incomplete dates

5.3.2.1. Disease history

Incomplete dates for disease history (e.g., initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.

- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant 's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant 's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the participant should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date), then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

5.3.3. Imputation rules for date of last contact and efficacy assessments

5.3.3.1. Date of last contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date among the following:

- All participant assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Last date of contact collected on the 'Survival Follow-up' eCRF for 'date last known alive' (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates
- Randomization date
- Withdrawal of consent date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.3.2. Death date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact
- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

5.3.3.3. Tumor assessments

All investigation dates (e.g., X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (e.g., X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.3.4. Date of start of new anti-cancer therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For participants who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing, then the imputed start date of new anti-cancer therapy is derived as follows:
  - <u>Start date of new anti-cancer therapy is completely missing</u>

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - <u>Only year (YYYY) for start of anti-cancer therapy is available</u>

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN imputed start date = 01JANYYYY

- Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.1.2.1 for general methodology.

6.1. Primary Endpoints

6.1.1. DLT for Phase 1b

6.1.1.1. Primary Analysis

DLT rate is calculated as the number of DLT-evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants in the DLT-observation period.

6.1.2. Phase 2

6.1.2.1. Sub-Study A - Durable Objective Response

6.1.2.1.1. Primary analysis

Durable ORR is calculated as the proportion of participants in the full analysis population with durable OR along with a 2-sided 95% CI for durable ORR using the Clopper-Pearson method. Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR for 10 months, or who die, have PD, or stop tumor assessments for any reason prior to reaching a CR or PR for 10 months will be counted as non-responders in the assessment of Durable OR. Each participant will have a durable objective response status (0: no durable OR; 1: durable OR).

Refer to Section 6.2.2 for assessment of response.

6.1.2.2. Sub-Study B - Objective Response

6.1.2.2.1. Primary analysis

ORR is calculated as the proportion of participants in FAS with confirmed OR along with a 2-sided 95% CI for ORR using the Clopper-Pearson method. Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, have PD, or stop tumor assessments for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: no OR; 1: OR).

Refer to Section 6.2.2 for assessment of response.

ORR will be presented by treatment arm B1, B2, B3 and overall where participants will be assigned to a relevant arm using PD-L1 expression determined by local assessment (refer to Section 3.4.1). ORR summary by PD-L1 expression using central assessment will also be presented.

6.2. Secondary Endpoint(s)

6.2.1. Safety endpoints

Refer to Section 6.6.

6.2.2. Efficacy endpoints

The following analyses will be based on the full analysis set by sub-study and treatment group. Assessment of response will be made using RECIST v1.1. Tumor-related endpoints will be analyzed based on investigator assessment.

6.2.2.1. Objective response as assessed by the Investigator per RECIST v1.1

Best overall response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the date of first dose of study treatment until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

BOR Based on Confirmed Responses:

- CR = at least two determinations of CR at least 4 weeks apart and before first documentation of PD
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR)
- SD (applicable only to participants with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 12 weeks after the date of first dose of study treatment (and not qualifying for CR, PR, SD or non-CR/non-PD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Participants who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of participants with OR in the analysis set.

ORR by treatment group will also be calculated along with the 2-sided 95% CI using the Clopper-Pearson method[3] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of participants with a confirmed BOR of CR, PR, SD, non-CR/non-PD (applicable only to participants with non-measurable disease at baseline), PD, and NE will be tabulated. Participants with confirmed BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the date of first dose of study treatment without further evaluable tumor assessments)
- PD too late (>12 weeks after the date of first dose of study treatment)

Special and rare cases where BOR is NE due to both SD of insufficient duration and late PD will be classified as 'SD too early' (i.e., SD of insufficient duration).

6.2.2.2. Tumor shrinkage from baseline

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point.

It will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created by treatment group.

These plots will display the best percentage change from baseline in the sum of the diameters of all target lesions for each participant with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.3. Duration of response

Duration of Response (DR) is defined, for participants with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause. If a participant has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 9.

DR (months) = [date of event or censoring– first date of OR +1]/30.4375

Table 9. Outcome and Event Dates for DR Analyses

Scenario	Date of event/censoring	Outcome
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rates at 6, 10, 12, 15, 18, and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) [2] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[6] (conftype=loglog default option in SAS Proc LIFETEST)

with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DR will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of participants with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

Table 10. DR Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy	Start of new anti-cancer therapy
2	Event after 2 or more missing or inadequate post-baseline tumor assessments	Event after 2 or more missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and [EOS present OR disposition page for any epoch after screening says participant will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

6.2.2.4. Time to response

Time to response (TTR) is defined, for participants with OR, as the time from the date of first dose of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

TTR (in months) = [first date of OR – date of first dose of study treatment +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.5. Progression-free survival

Progression-Free Survival (PFS) is defined as the time from the date of first dose of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death), for participants who start a new anti-cancer therapy

prior to an event (see Section 5.2.6) or for participants with an event after 2 or more missing tumor assessments. Participants who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment will be censored on the date of first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment (i.e. ≤ 16 weeks after the first dose of study treatment) in which case the death will be considered an event.

The censoring and event date options to be considered for the PFS analysis are presented in Table 11.

PFS (months) = [date of event or censoring– date of first dose of study treatment +1]/30.4375

Table 11. Outcome and Event Dates for PFS Analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of first dose of study treatment [a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the participant dies ≤16 weeks after the first dose of study treatment and did not initiate new anti-cancer therapy, the death is an event with date on death date.

If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the first dose of study treatment; if the criteria were met the censoring will be on the date of the first dose of study treatment.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median PFS time with 2-sided

95% CIs. In particular, the PFS rates at 6, 9, 12, 18, and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[2] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[6] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 12 following the hierarchy shown.

Table 12. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/ first dose of study treatment	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ first dose of study treatment OR End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any epoch after screening says participant will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The PFS time or censoring time and the reasons for censoring will also be presented in a participant listing.

Time of Follow-Up for PFS

A plot will be generated to compare planned and actual relative day of tumor assessments by treatment group. A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the PFS censoring and event indicators.

6.2.2.6. Overall Survival

Overall survival (OS) is defined as the time from the first dose of study treatment to the date of death due to any cause. Participants last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– date of first dose of study treatment

+1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented by sub-study and treatment group together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rates at 6, 9, 12, 15, 18, and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[2] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002) [66] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of participants with an event (death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 13 following the hierarchy shown.

Table 13. OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [withdrawal of consent date ≥ first dose of study treatment OR End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
2	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 16 weeks]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

The OS time or censoring time and the reasons for censoring will also be presented in a participant listing.

Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the OS censoring and event indicators.

6.2.3. Pharmacokinetic endpoints

The following pharmacokinetic analyses will be based on the PK concentration analysis set by treatment group.

Concentrations for sasanlimab will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by treatment group, cycle and day, and/or nominal time.

Individual participant and median profiles of the concentration-time data will be plotted by treatment group using nominal times, as appropriate. Median profiles may be presented as appropriate.

Trough concentrations (C_{trough}) for sasanlimab will be plotted using a box-whisker plot by treatment group, cycle and day.

Concentrations for encorafenib, binimetinib (Sub-Study A), axitinib, SEA-TGT (Sub-Study B) and any analyzed metabolites will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by treatment group/dose, cycle, timepoint, and day (as applicable). Exclusions or separate summaries for dose modifications and concomitant medications may be considered in data summaries.

C_{trough} for encorafenib, binimetinib and applicable metabolites will be plotted for each treatment group, and/or dose level using a box whisker plot by cycle and day.

Trough concentrations (C_{trough}) will be directly observed from the respective concentration-time data. Dose-normalized PK parameters (C_{trough}-DN) may be reported, as appropriate.

6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association of drug exposure such as sasanlimab, encorafenib, and/or binimetinib including applicable metabolite(s) with biomarker levels or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

6.2.5. Biomarker endpoints

The following biomarker analyses will be based on the biomarker analysis set by treatment group.

Descriptive statistics for levels of PD-L1 expression, and number and percentage of participants with tumors categorized with baseline PD-L1 expression level high versus low will be presented by treatment group. Expression level will be provided prior to database release. Summaries of BOR will be presented by treatment group and by PD-L1 status.

For Sub-Study B, the above analyses will be conducted for local and central PD-L1 expression assessments including summary of concordant and discordant assessments.

6.2.6. Endpoints for immunogenicity data

The following immunogenicity analyses of sasanlimab for Sub-Study A and Sub-Study B, and for SEA-TGT for Sub-Study B only will be based on the immunogenicity analysis set by treatment group.

All analyses described below are performed by treatment group and for all treatment groups combined within a study, if deemed appropriate.

Blood samples for sasanlimab immunogenicity testing will be collected pre-dose on Cycle 1, 2, 3, 4 (Sub-Study B only), 5, 7, 10, and 13 and then every 6 cycles until EOT. All samples should be drawn within 6 hours before start of sasanlimab dosing. Additional samples for anti-sasanlimab and anti-SEA-TGT (Sub-Study B only) antibodies (and simultaneous PK

draws for measurement of respective study drugs) will be collected at the Day 30 Follow-up visit after the end of treatment.

Samples positive for ADA will be analyzed for titer and may be analyzed for nAb.

For the immunogenicity data, the percentage of participants with positive ADA and Nab each will be summarized by treatment. For participants with positive ADA or Nab, the magnitude (titer), time of onset, and duration of ADA or Nab response will also be described, if data permit.

Participants will be characterized into different ADA categories based on the criteria defined in Table 14.

Table 14. Participants Characterized Based on Anti-Drug Antibody Results (ADA Status) Category

Term	Definition
ADA-positive sample	ADA sample titer ≥ Log10 (99)
ADA-negative sample	ADA sample titer <Log10 (99)
NAb-positive sample	NAb sample titer ≥ Log10 (4)
NAb-negative sample	NAb sample titer < Log10 (4)
Pre-existing ADA/NAb	Positive ADA/NAb at baseline (e.g. day 1 pre-dose)
Cross-reactivity	This often refers to immunogenicity testing against an endogenous antigen, biosimilar reference product or another biotherapeutic within the same therapeutic class.
Subject-level immunogenicity analysis population	
ADA evaluable population	All subjects with ≥ 1 post-treatment ADA result.
NAb evaluable population	ADA-positive subjects with ≥ 1 post-treatment NAb result, plus all ADA-negative subjects. An ADA-positive subject without any post-treatment NAb data is excluded from the analysis population.
Subject-level definitions	
Treatment-induced ADA	Baseline ADA titer is missing or negative and subject has ≥ 1 post-treatment positive ADA titer.
Treatment-boosted ADA	Baseline ADA titer is positive and subject has a ⩾ 4-fold dilution increase in ADA titer from baseline in ≥ 1 post-treatment sample. Since the ADA titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline.
ADA-positive subject	A subject with ≥ 1 treatment-induced or treatment-boosted ADA response.
ADA-negative subject	An ADA evaluable subject without treatment-induced or treatment-boosted ADA response. Subject either has (1) all ADA-negative results throughout the study or (2) is ADA positive at baseline but did not become treatment-boosted post dose.
ADA incidence	The percent of ADA-positive subjects in a treatment group/cohort or study.
Treatment-induced NAb	Baseline NAb titer is missing or negative or ADA-negative and subject has ≥ 1 post-treatment positive NAb titer.
Treatment-boosted NAb	Baseline NAb titer is positive and subject has a ⩾ 4-fold dilution increase in NAb titer from baseline in ≥ 1 post-treatment sample. Since NAb titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline.
NAb-positive subject	An ADA-positive subject with ≥ 1 treatment-induced or treatment-boosted NAb response. For ADA-positive (treatment-boosted) subjects, subject is NAb positive only if the subject has ≥1 treatment-induced or treatment-boosted NAb response at the visit where the subject has a treatment-boosted ADA response. For visits where the subject did not show a boosted ADA response, the subject is classified as NAb-negative for the visit even if the subject has post-treatment positive NAb titer for that visit.
NAb-negative subject	(1) an ADA-negative subject or (2) an ADA-positive subject without treatment-induced or treatment-boosted NAb response (i.e. subject has all NAb-negative results throughout the study or subject is NAb positive at baseline but did not become treatment-boosted post dose).
NAb incidence	The percent of NAb-positive subjects in a treatment group/cohort or study.
Duration of ADA and NAb response (subject-level definitions):	
Transient ADA	An ADA-positive subject with (1) a treatment-induced or treatment-boosted ADA sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted ADA samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is ADA negative.

Term	Definition
Persistent ADA	An ADA-positive subject with first and last positive ADA samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between.
Indeterminate ADA	An ADA-positive subject who is not persistent or transient.
Transient NAb	A NAb-positive subject with (1) a treatment-induced or treatment-boosted NAb sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted NAb samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is NAb negative or ADA negative.
Persistent NAb	A NAb-positive subject with first and last positive NAb samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between.
Indeterminate NAb	A NAb-positive subject who is not persistent or transient.

Note: Duration of response (persistent, transient or indeterminate) definitions are only applicable to ADA (or NAb)-positive subjects.

The number and percentage of participants in each ADA and nAb category will be summarized.

All ADA and NAb data will be listed, and the number and percentage of participants in each ADA and NAb category will be summarized by treatment arm and overall. Incidence of ADA and NAb positive participants and time to first ADA and NAb detection will also be summarized by treatment group and overall. Data from samples collected at EOT will be presented in individual listings, but only data from EOT samples collected within 30 days of last dose of the respective agent and at predose (if the last dose was given at EOT visit) will be included in categorical assessments and summaries.

6.2.7. Patient Reported Outcomes endpoints

6.2.7.1. Sub-Study A

At each time point, the number and percentage of participants who complete the EORTC QLQ-C30 and EORTC QLQ-LC13 will be summarized, as will the reasons for non-completion of these measures. An instrument is considered complete if at least one item was answered by the participant.

Summary statistics (mean and standard deviation [SD], median, range, and 95% CI) of absolute scores will be reported using line charts for each of the functional, symptoms and overall quality of life subscales/items of the EORTC QLQ-C30 and the EORTC QLQ-LC13. The mean change from baseline with 95% CI will also be reported by time point. Line charts depicting the means and changes from baseline along with 95% CIs over time for each instrument will be produced.

6.2.7.2. Sub-Study B

There will be no analysis of PRO endpoints in Sub-Study B.

6.3. Other Endpoints

- Exploratory biomarker data will be analyzed based on the biomarker analysis sets as defined in Section 4 and as described in Section 6.2.5.

If data permits, appropriate descriptive statistics will be provided for the exploratory endpoints which will include DNA, RNA, and protein markers that may be relevant to the

- Depth of Response

- A Deep Response is defined as a confirmed response per RECIST v1.1 with a depth of response of at least 50%. The Deep response rate will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method[3] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option) by treatment group and based on the full analysis set.

6.4. Subset Analyses

Applicable to Phase 2 only.

Durable OR (Sub-Study A only) and OR will be summarized in the following subsets within each treatment group:

- Pooled Geographical Region
  - North America
  - Europe
  - Asia
  - Rest of World (ROW)
- Age
  - Age < 65 years
  - Age ≥ 65 years
- Gender
  - Male
  - Female
- Race
  - White
  - Asian
  - Black or African American
  - Other
- ECOG PS
  - 0
  - ≥1

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

The following analyses will be based on the FAS overall and separately by Sub Study and treatment group.

6.5.1.1. Demographic characteristics

Demographic characteristics will be summarized by treatment group using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown
  - Ethnic origin:
    - Hispanic or Latino
    - Not Hispanic or Latino
  - Age (years): summary statistics
  - Age categories:
    - < 65 years, ≥ 65 years
    - < 65, 65-<75, 75-<85, ≥ 85 years
  - Pooled Geographical Region (as applicable):
    - North America
    - Europe
    - Asia
    - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including > 10% of the overall treated population)
  - Geographic Region (as applicable):
    - North America
    - Latin America
    - Western Europe
    - Eastern Europe
    - Middle East
    - Australasia
    - Asia
    - Africa

- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4

Center codes will be used for the determination of the participant's geographic region.

The listing of demographics and baseline characteristics will include the following information: participant identifier, treatment group, age, sex, race, ethnicity and ECOG performance status.

6.5.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Significant Medical History' and "Medical History" eCRF page. Medical history will be summarized as the numbers and percentages of participants by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease characteristics

Information on disease characteristics collected on 'Primary Diagnosis', 'Substance Use'and RECIST eCRF pages will be summarized overall and by treatment group. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Site of primary tumor
- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page)
- Time since initial diagnosis to date of first dose of study treatment (months), defined as (date of first dose of study treatment – date of initial diagnosis)/30.4375

From the RECIST eCRF page:

- Measurable disease (lesions) at baseline (Yes, No)
- Involved tumor sites at baseline

From the 'Substance Use' eCRF page:

- Smoking history (never smoker vs current vs former smoker)

Listing of disease history will be provided with all relevant data (as collected on the 'Primary Diagnosis' eCRF page) and derived variables as above. Brain metastasis at baseline will be reported as yes/no.

6.5.1.4. Prior anti-cancer therapies

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one type of prior anti-cancer therapy
- Participants with at least one prior anti-cancer drug therapy
- Participants with at least one prior anti-cancer radiotherapy
- Participants with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer drug therapy regimens: missing, 1, 2, 3, ≥4
- Prior anti-cancer immune therapy (including PD-1 and PD-L1)
- Intent of Drug Therapy: Neo-Adjuvant, Adjuvant, Advanced – Metastatic, Local regional Disease-Recurrence
- Best response: CR, PR, SD, PD, Unknown, Not applicable. Best response is derived from the last treatment regimen.

The prior anti-cancer drugs will also be summarized based on the number and percentage of participants by the drug class and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer drug therapies will be included in the listing that follow with a flag to identify prior therapies. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies

6.5.2. Study conduct and participant disposition

The following analyses will be performed based on the FAS overall and separately by treatment group.

6.5.2.1. Participant disposition

The percentages below will be calculated based on the number of participants in the FAS.

- Total number of participants screened overall

- Number of participants who discontinued from the study prior to treatment with study drug overall and by the main reason for discontinuation
- Number and percentage of treated participants in each of the analysis sets defined in Section 4
- Number and percentage of participants with study drug ongoing (separately for each study drug administered in a combination)
- Number and percentage of participants who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug administered in a combination)
- Number and percentage of participants who entered follow-up
- Number and percentage of participants who discontinued follow-up overall and by the main reason for discontinuation

In addition, the following will be summarized:

- Number and percentage of treated participants overall, by region (Europe, EEA (required by EudraCT), North America, Asia, Australia), by country within region
- Number and percentage of treated participants by center

A listing of participant discontinuations related to COVID-19 will be presented.

A listing of all participants affected by COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the participants and/or the conduct of the study and/or its evaluation will be reported. These include:

- Participants who are dosed on the study despite not satisfying the inclusion criteria
- Participants who develop withdrawal criteria whilst on the study but are not withdrawn
- Participants who receive the wrong treatment or an incorrect dose
- Participants who receive an excluded concomitant medication
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

A listing of Protocol Deviations related to COVID-19 will be provided.

6.5.3. Study treatment compliance and exposure

The following analyses will be based on the safety analysis set by treatment group.

Exposure may be summarized as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The information that will be summarized depends on how the study drug is dosed (e.g., infusion cyclical, oral daily, oral cyclical).

The formulae below should be applied to each study drug separately even when study drugs are administered in combination.

For Sub-Study A, the derivations below are provided assuming 1 cycle = 4 weeks and for the following study drugs:

- Sasanlimab administration: SC Q4W at a dose of 300 mg. Doses of sasanlimab may be recorded in the eCRF as 300 mg, 0 mg, or 'Unknown'. An 'Unknown' dose amount should not be considered a 0 mg dose and must be included in the derivations for first and last dose of study drug.
- Encorafenib administered orally QD PO as a dose of 300 or 450 mg in 4 week cycles.
- Binimetinib administered orally BID PO at a dose of 30 or 45 mg in 4 week cycles.

For Sub-Study B, the derivations below are provided assuming 1 cycle = 3 weeks and for the following study drugs:

- Sasanlimab administration: CCI at a dose of CCI Doses of sasanlimab may be recorded in the eCRF as actual dose given in mg.
- Axitinib administered orally BID PO as a dose of 5 mg or 3 mg in 3 week cycles.
- SEA-TGT administered IV at a dose (mg/kg) of DL0, DL1, or DL-1 in 3 week cycles

6.5.3.1. Exposure to Sasanlimab

Sub-Study A: Duration of exposure to Sasanlimab (weeks) =

(last dose date of sasanlimab – first dose date of sasanlimab +28)/7

Sub-Study B: Duration of exposure to Sasanlimab (weeks) =

(last dose date of sasanlimab – first dose date of sasanlimab +21)/7

The median and range of non-zero doses of sasanlimab received by a participant will be provided.

The summary of exposure to sasanlimab will include:

- Duration of exposure to sasanlimab (weeks)

- Doses received for sasanlimab

6.5.3.2. Exposure to encorafenib

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with encorafenib (weeks) = (end date – date of first dose of encorafenib +1)/7,

where end date = date of last dose of **encorafenib**

Duration of exposure to encorafenib (weeks) =

(last dose date of **encorafenib** – first dose date of **encorafenib** + 1)/7

Cumulative dose is the sum of the actual doses of **encorafenib** received in the study.

Actual Dose Intensity (DI)

- Actual DI (mg/week) = [cumulative dose (mg)] / [intended duration of treatment (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of study drug to last dose of study drug]

  = 100 × [cumulative dose] / [7 × d × duration of exposure to encorafenib (weeks)]

  Where d= 300 mg or 450 mg

The summary of exposure to encorafenib will include:

- Duration of exposure to encorafenib (weeks)
- Cumulative Dose (mg)
- Actual DI (mg/week)
- RDI (%)

6.5.3.3. Exposure to binimetinib

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with binimetinib (weeks) = (end date – date of first dose of binimetinib +1)/7,

where end date = date of last dose of **binimetinib**

Duration of exposure to binimetinib (weeks) =

(last dose date of **binimetinib** – first dose date of **binimetinib** + 1)/7

Cumulative dose is the sum of the actual doses of **binimetinib** received in the study.

Actual Dose Intensity (DI)

- Actual DI (mg/week) = [cumulative dose (mg)] / [intended duration of treatment (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of study drug to last dose of study drug]

  = 100 × [cumulative dose] / [7 ×2 × d × duration of exposure to binimetinib in weeks]

  where d= 30 mg or 45 mg

The summary of exposure to binimetinib will include:

- Duration of exposure to binimetinib (weeks)
- Cumulative Dose (mg)
- Actual DI (mg/week)
- RDI (%)

6.5.3.4. Exposure to axitinib

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with axitinib (weeks) = (end date – date of first dose of axitinib +1)/7,

where end date = date of last dose of **axitinib**

Duration of exposure to axitinib (weeks) =

(last dose date of **axitinib** – first dose date of **axitinib** + 1)/7

Cumulative dose (mg) is the sum of the actual doses of **axitinib** received in the study.

Actual Dose Intensity (DI)

- Actual DI (mg/week) = [cumulative dose (mg)] / [intended duration of treatment (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of study drug to last dose of study drug]

  = 100 × [overall cumulative dose] / [7 ×2 × d × duration of exposure to axitinib in weeks]

  where d= 5 mg or 3 mg

The summary of exposure to axitinib will include:

- Duration of exposure to axitinib (weeks)

- Cumulative Dose (mg)
- Actual DI (mg/week)
- RDI (%)

6.5.3.5. Exposure to SEA-TGT

The dose level is calculated as actual dose administered (mg/kg).

Intended duration of treatment with SEA-TGT (weeks) = (end date – date of first dose of SEA-TGT +21)/7,

where end date = date of last dose of **SEA-TGT**

Duration of exposure to SEA-TGT (weeks) =

(last dose date of SEA-TGT – first dose date of SEA-TGT +21)/7

Cumulative dose (mg/kg) is the sum of the actual doses of SEA-TGT received overall

Actual Dose Intensity (DI)

- Actual DI (mg/week/3-week cycle) = [cumulative dose (mg/kg)] / [intended duration of treatment with SEA-TGT (weeks)/3]

Relative Dose Intensity (RDI)

- Intended DI (mg/kg/3-week)=[intended comulative dose per cycle]/[3-week cycle]=DLX (mg/kg/3-week cycle)
- RDI (%) = 100 × [actual DI] / [intended DI] = 100 × [actual DI] / [DLX (mg/kg/3-week cycle)]

Where DLX is assigned dose of SEA-TGT in mg/kg (DL1, DL0, or DL-1)

The median and range of non-zero doses of SEA-TGT received by a participant will be provided.

The summary of exposure to SEA-TGT will include:

- Duration of exposure to SEA-TGT (weeks)
- Total number of infusions received for SEA-TGT
- Cumulative Dose (mg/kg)
- Actual DI (mg/kg/3-week cycle)
- RDI (%)

6.5.3.6. Dose reductions

Applicable to encorafenib (Sub-Study A), binimetinib (Sub-Study A), sasanlimab, axitinib (Sub-Study B) and SEA-TGT (Sub-Study B). Dose reduction is defined as a change to a non-zero dose level lower than that planned in the protocol.

Applicable to sasanlimab. In Sub-Study A the dose for sasanlimab in Sub-Study A can be entered as 0, 300 mg or 'partial dose'. Where a 'partial dose' is a captured as "UNK" on the sasanlimab CRF dosing page. The number and percentage of participants with at least one 'partial dose' dose amount as well as a breakdown of the number of unknown dose amounts (1, 2, 3, 4, 5, ≥6) will be summarized. In Sub-Study B, the actual dose for sasanlimab in mg is captured on eCRF and any non-zero dose less than planned CCI will be summarized as dose reduction.

The number and percentage of participants with at least one dose reduction as well as a breakdown of the number of dose reductions (1, 2, 3, ≥4) will be summarized.

6.5.3.7. Dose interruptions

Applicable to encorafenib (Sub-Study A), binimetinib (Sub-Study A), and axitinib (Sub-Study B)

An interruption is defined as a 0 mg dose administered on one or more days for encorafenib, binimetinib, or axitinib. What follows defines how dose interruptions will be counted in the case of multiple dose interruptions.

- If an interruption occurs consecutively for at least two days, then it will be counted only once (example: If the actual dose on days 1-3 is 30 mg and actual dose on days 4-5 is 0 mg and dose interruption on days 4-5 is due to AE, then the total number of dose interruptions is 1).
- If an interruption occurs for more than one day but the days are not consecutive, ie there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (example: If the actual dose on days 1, 3 and 5, is 30 mg and actual dose on days 2 and 4 is 0 mg the total number of dose interruptions is 2).

A dose interruption is not considered a dose reduction.

The number and percentage of participants with dose interruptions and the corresponding reasons will be summarized.

6.5.3.8. Dose delays

Applicable to sasanlimab and SEA-TGT (Sub-Study B).

Dose Delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses. 'Unknown' dose amounts for sasanlimab are considered a non-zero dose.

- Sub-Study A: Dose Delay for Dose x (days) = Date of Dose x – Date of Dose (x-1) – 28

- Sub-Study B: Dose Delay for Dose x (days) = Date of Dose x – Date of Dose (x-1) – 21

Dose delays will be grouped into the following categories:

- No delay
- 1-2 days delay
- 3-6 days delay
- 7 or more days delay

For example, for sasanlimab, administered on a 4-week schedule, if one participant receives sasanlimab on Day 1, then the next sasanlimab administration date will be on Day 29 however, if the participant receives sasanlimab at Day 30 or 31 this is considered as 1-2 days delay.

No delay and 1-2 days delay will also be summarized together.

The number and percentage of participants with delayed study drug administration and maximum length of delay, i.e., the worst case of delay if participants have multiple dose delays will be summarized.

6.5.4. Concomitant medications and non-drug treatments

The following analyses will be based on the safety analysis set by treatment group.

Concomitant medications are medications, other than study drugs, which started prior to first dose date of study treatment and continued during the on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study drugs and pre-medications for study drug, which are started before the first dose of study treatment.

Concomitant medications will be summarized from the ‘Concomitant Medications’ eCRF page.

Summary of concomitant medications will include the number and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under ‘Unavailable ATC classification’ category.

6.5.5. Subsequent anti-cancer therapies

The following analyses will be based on the full analysis set by treatment group.

Anti-cancer drug treatment will be provided in a data listing with data retrieved from 'Follow-up Cancer Therapy' eCRF page.

Number and percentage of participants with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up Cancer Therapy', 'Radiation Therapy' and 'On Study and Follow-up Cancer Surgery' eCRF pages.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the safety analysis set by treatment group.

6.6.1. Adverse events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period as defined in Section 3.5.1.

All analyses described will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (i.e., no answer to the question 'Relationship with study treatment'). Related AEs are those related to any study drug (i.e., at least one of the study drugs).
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Dose Reduction:** adverse events leading to dose reduction of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Dose reduced).
- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted). The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted).
- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan [SRP] and finalized for analysis of the current study data prior to DB lock)

Unless otherwise specified, AEs will be summarized by number and percentage of participants with the AE in the category of interest as described above, by treatment group, primary SOC and PT in decreasing frequency based on the frequencies observed for Dose level 0 of Phase1b.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All adverse events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following by treatment group as applicable:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to dose reduction of sasanlimab
  - TEAEs leading to dose reduction of encorafenib
  - TEAEs leading to dose dose reduction of binimetinib
  - TEAEs leading to dose reduction of axitinib
  - TEAEs leading to dose reduction of SEA-TGT
  - TEAEs leading to interruption of sasanlimab
  - TEAEs leading to interruption of encorafenib
  - TEAEs leading to interruption of binimetinib
  - TEAEs leading to interruption of axitinib
  - TEAEs leading to interruption of SEA-TGT
  - TEAEs leading to discontinuation of sasanlimab
  - TEAEs leading to discontinuation of encorafenib

  - TEAEs leading to discontinuation of binimetinib
  - TEAEs leading to discontinuation of axitinib
  - TEAEs leading to discontinuation of SEA-TGT
  - TEAEs leading to discontinuation of all study drugs
  - Related TEAEs leading to discontinuation of sasanlimab
  - Related TEAEs leading to discontinuation of encorafenib
  - Related TEAEs leading to discontinuation of binimetinib
  - Related TEAEs leading to discontinuation of axitinib
  - Related TEAEs leading to discontinuation of SEA-TGT
  - Related TEAEs leading to discontinuation of all study drugs
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death
  - irAEs
- TEAEs by SOC and PT and worst grade
- TEAEs related to any study drug by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT

6.6.1.2. Adverse events leading to dose reduction

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to dose reduction of each study drug by treatment group as applicable:

- TEAEs leading to dose reduction of encorafenib by SOC and PT
- TEAEs leading to dose reduction of binimetinib by SOC and PT
- TEAEs leading to dose reduction of axitinib by SOC and PT
- TEAEs leading to dose reduction of SEA-TGT by SOC and PT

The listing of all AEs leading to dose reduction will also be provided with the relevant information.

6.6.1.3. Adverse events leading to interruption of study treatment

AEs leading to interruption will be defined as AEs identified in the AE eCRF page with an action taken with study treatment of 'drug interrupted'.

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment group:

- TEAEs leading to interruption of sasanlimab by SOC and PT
- TEAEs leading to interruption of encorafenib by SOC and PT
- TEAEs leading to interruption of binimetinib by SOC and PT
- TEAEs leading to interruption of axitinib by SOC and PT
- TEAEs leading to interruption of SEA-TGT by SOC and PT

The listing of all AEs leading to interruption of study treatment will also be provided with the relevant information.

In addition, the frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment group:

- TEAEs leading to both interruption and dose reduction of encorafenib by SOC and PT
- TEAEs leading to both interruption and dose reduction of binimetinib by SOC and PT
- TEAEs leading to both interruption and dose reduction of axitinib by SOC and PT
- TEAEs leading to both interruption and dose reduction of SEA-TGT by SOC and PT

This summary will take into account PTs with both actions as defined in Section 6.6.1, even though the actions may be captured for different PT records (i.e., different onset for the PT with action "drug interrupted" and the PT with action "dose reduced").

6.6.1.4. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment group:

- TEAEs leading to discontinuation of sasanlimab by SOC and PT
- TEAEs leading to discontinuation of encorafenib by SOC and PT
- TEAEs leading to discontinuation of binimetinib by SOC and PT
- TEAEs leading to discontinuation of axitinib by SOC and PT
- TEAEs leading to discontinuation of SEA-TGT by SOC and PT

- Related TEAEs leading to discontinuation of sasanlimab by SOC and PT
- Related TEAEs leading to discontinuation of encorafenib by SOC and PT
- Related TEAEs leading to discontinuation of binimetinib by SOC and PT
- Related TEAEs leading to discontinuation of axitinib by SOC and PT
- Related TEAEs leading to discontinuation of SEA-TGT by SOC and PT
- TEAEs leading to discontinuation of all study drugs by SOC and PT
- Related TEAEs leading to discontinuation of all study drugs by SOC and PT

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

6.6.2. Deaths

The frequency (number and percentage) of participants in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs, by treatment group.

- All deaths
- Deaths within 30 days after last dose of study treatment
- Reason for Death
  - Disease under study
  - Study treatment toxicity
  - Unknown
  - Other.

In addition, date and cause of death will be provided in individual participant data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.
- Flag for deaths related to COVID-19.

6.6.3. Serious adverse events

The frequency (number and percentage) of participants with each of the following will be presented for treatment-emergent SAEs by treatment group:

- SAEs by SOC and PT

- Related SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.6.4. Other significant adverse events

The frequency (number and percentage) of participants with each of the following will be presented for irAEs, by treatment group:

- irAEs leading to death, by Cluster and PT
- irAEs, by Cluster and PT
- irAEs, Grade ≥ 3, by Cluster and PT
- irAEs leading to discontinuation of sasanlimab, by Cluster and PT
- irAEs leading to discontinuation of all study drugs, by Cluster and PT
- Serious irAEs, by Cluster and PT

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period.

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (e.g., hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Abnormalities classified according to NCI-CTCAE toxicity grading v.5.0 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

$$\text{Derived differential absolute count} = (\text{WBC count}) \times (\text{Differential \%value} / 100)$$

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 800/mm3
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN .

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing) will be provided.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of participants evaluable for CTCAE grading (ie those participants for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.
- The number and percentage of participants with newly occurring or worsening laboratory abnormalities during the on-treatment period will be summarized by worst grade on-treatment (Grade 1, 2, 3, 4, Grade 3/4 and any grade [Grades 1-4]).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE.

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of participants with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period

6.6.5.2. Other laboratory parameters

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

6.6.6. Electrocardiogram

QTcB and QTcF will be derived based on RR and QT (see below). The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions. If QTcB and QTcF methods do not adequately correct for HR and there are a sufficient number of participants (eg >30) with baseline ECGs, an alternate correction to achieve the goal of getting uncorrelated QTc and RR is based on a linear regression method which yields, theoretically, uncorrelated QTc and RR.

Linear regression method:

- Fit a model QT = a + b × RR to baseline data
- Use the estimated slope, $\hat{b}$, to correct QT
- Corrected QT for heart rate will be computed as follows:

$$QTcP = QT + \hat{b} \times (1 - RR)$$

Data will be summarized using QTcF and QTcB. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcP.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) by treatment group, during the on-treatment period. The denominator to calculate percentages for each category is the number of participants evaluable for the category.

- Pearson correlation between QT and HR, QTc (QTcB, QTcF and, if applicable, QTcP) and HR using individual (non-averaged) baseline assessments
- Frequency (number and percentage) of participants with notable ECG values according to the following categories:
  - QT/QTc increase from baseline >30 ms, >60 ms
  - QT/QTc > 450 ms, > 480 ms, > 500 ms
  - HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
  - HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
  - PR ≥ 220 ms and increase from baseline ≥ 20 ms
  - QRS ≥ 120 ms

Participants with notable ECG interval values and qualitative ECG abnormalities will be listed for each participant and time point and the corresponding notable values and abnormality findings will be included in the listings.

6.6.7. Physical examination

Abnormal and clinically significant physical exam findings will be reported as AEs.

7. INTERIM ANALYSES

7.1. Sub-Study A

A futility analysis based on ORR will be performed in Phase 2 to allow early termination for futility after 30 participants are treated and followed for 2 on-treatment assessments (~4 months), without holding participant enrollment. If based on the observed ORR the probability of a true ORR ≥48% is ≤0.10, then the study will be stopped for futility. For example, the study will be stopped for futility if ≤10 confirmed ORs are observed in the first 30 participants treated.

The probability of stopping the sub-study (if ≤10 confirmed ORs are observed in the first 30 participants treated) under the alternative hypothesis is 0.014.

7.2. Sub-Study B

There will be no interim analysis in Sub-Study B.

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9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the SRP for sasanlimab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 15. Unless otherwise noted, this case definition is hierarchical, i.e., each step is only checked for participants and events that have already met the prior step.

Table 15. Case Definition for irAEs

Step	Selection Criteria	
1	Adverse Event (AE) selected based on a list of pre-specified MeDRA PTs within clusters. These are included in the SRP. If AE matches the list, then it is included in the next step.	
2	AE onset on or after the first dose of study drug and on or before 90 days after last dose of study drug.	This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications.
3	AE treated with corticosteroids or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement.	Look in the conmed pages for AEs where concomitant medications match any of the following A) conmed ATC code is in (H02A, H02B, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters. B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies" C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus"

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (e.g., addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

Appendix 2. BLRM (Sub-Study A)

Detailed Dose Escalation/De-escalation Scheme for BLRM Design for Sasanlimab + Encorafenib + Binimetinib

This section provides the details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model for the encorafenib, binimetinib, and sasanlimab triplet combination.

Statistical Model

The statistical model for combination dose-DLT data comprises single-agent toxicity parts, and interaction parts. The single-agent toxicity parts allow the incorporation of single-agent toxicity data

Single-Agent Parts

Let $\pi_1(d_1)$ be the risk of DLT for encorafenib given as a single agent at dose d_1; $\pi_2(d_2)$ be the risk of DLT for binimetinib given as a single agent at dose d_2; and $\pi_3(d_3)$ be the risk of DLT for sasanlimab given as a single agent at dose d_3. These single agent dose-DLT models are 2 parameter logistic regression models:

encorafenib: $\text{logit}\big(\pi_1(d_1)\big) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

binimetinib: $\text{logit}\big(\pi_2(d_2)\big) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

sasanlimab: $\text{logit}\big(\pi_3(d_3)\big) = \log(\alpha_3) + \beta_3 \log(d_3/d_3^*)$

where d_1^*=450 mg, d_2^* =45 mg, and d_3^* =300 mg are used to scale the doses of encorafenib, binimetinib, and sasanlimab, respectively. Hence, α_1, α_2 , and α_3 (all >0) are the single-agent odds of a DLT at d_1^* mg, d_2^* mg, and d_3^* mg, respectively; and β_1, β_2, and β_3(all >0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

Interaction Parts

Under an assumption that there is no interaction, the risk of a DLT at dose d_1 of encorafenib, dose d_2 of binimetinib, and dose d_3 of sasanlimab is:

$$\pi_{123}^{0}(d_1, d_2, d_3) = 1 - \big(1 - \pi_1(d_1)\big)\big(1 - \pi_2(d_2)\big)\big(1 - \pi_3(d_3)\big)$$

To model the interaction between encorafenib, binimetinib, and sasanlimab, the following 4 odds multipliers are introduced.

η_{12}: 2-way interaction between encorafenib and binimetinib

η_{13}: 2-way interaction between encorafenib and sasanlimab

η_{23}: 2-way interaction between binimetinib and sasanlimab

η_{123}: 3-way interaction between encorafenib, binimetinib, and sasanlimab

The risk of DLT for combination dose (d_1, d_2, d_3) is then given by:

$$\text{odds}\big(\pi_{123}(d_1, d_2, d_3)\big) = g(\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}) \times \text{odds}\big(\pi_{123}^{0}(d_1, d_2, d_3)\big)$$

$$\begin{aligned} g(\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}) = \ & \exp(\eta_{12} \times d_1/d_1^* \times d_2/d_2^*) \\ & \times \exp\,(\,\eta_{13} \times d_1/d_1^* \times d_3/d_3^*) \\ & \times \exp\,(\eta_{23} \times d_2/d_2^* \times d_3/d_3^*) \\ & \times \exp\,(\eta_{123} \times d_1/d_1^* \times d_2/d_2^* \times d_3/d_3^*) \end{aligned}$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; η_{ij} is the log-odds ratio between the interaction and no interaction model at the reference doses of drug i and j and a zero dose of the third drug. For example, η_{23} is the log-odds ratio between the interaction and no interaction model at encorafenib = 0 mg, binimetinib = 45 mg and sasanlimab = 300 mg. Therefore, $\eta_{12} + \eta_{13} + \eta_{23} + \eta_{123}$ is the log-odds ratio between the interaction and no interaction model at the reference doses for all 3 drugs. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity, respectively.

Inclusion of the Doublet Data

Based on the preliminary data from the Phase 1b part of study CMEK162X2110, a total 47 participants were enrolled at the starting dose level of 45 mg for binimetinib in combination with escalating doses of encorafenib (ranging from 50 mg to 800 mg). Forty-four (44) participants were DLT-evaluable. This information from study CMEK162X2110 was incorporated in the assessment of prior distribution of DLT, starting dose, data scenarios, and simulations of triplet via a direct down-weighting approach. The weight was calculated using the formula below assuming moderate heterogeneity between the populations included in the binimetinib + encorafenib doublet and triplet in terms of DLT;

$$w = \frac{1}{1 + \frac{2\tau^2}{\sigma^2} N}$$

where, N= Total number of participants enrolled in the CMEK162X2110 (N=44)

σ = population standard deviation (σ =2)

τ = heterogeneity between populations in the CMEK162X2110 and current trial (τ =0.25)

Prior Specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for ecorafenib, $\log(\alpha_2)$, $\log(\beta_2)$ for binimetinib, $\log(\alpha_3)$, $\log(\beta_3)$ for sasanlimab, and the interaction parameters $\eta = (\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123})$. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters.

Prior Distribution for the Logistic Parameters for Single Agent

This section illustrates the derivation of prior distributions for single agent model parameters ($\log(\alpha_s)$, $\log(\beta_s)$)'s using the available single agent dose-DLT information via a MAP approach.

Description of the Meta-Analytic-Predictive Approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ of the new trial using DLT data from historical studies. Let r_{ds} and n_{ds} be the number of participants with a DLT, and the total number of participants at dose d in historical trial s ($s = 1, \ldots, \langle S \rangle$). The corresponding probability of a DLT is π_{ds}. The model specifications are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Binomial}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) \ + \ \beta_s \log(d/d^*)$$

$$\left(log(\alpha_s), log(\beta_s)\right) \mid \mu, \psi_{g(s)} \sim \text{Bivariate Normal (BVN)}\left(\mu, \psi_{g(s)}\right), \qquad \text{s} = 1, \ldots, \langle S \rangle$$

$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi_{g\,(*)} \sim \text{BVN}\left(\mu, \psi_{g\,(*)}\right)$$

The historical trials are partitioned into $\langle G \rangle$ exchangeability groups, with the exchangeability group membership of historical trial s being represented by $g(s)$. The new trial is assigned to exchangeability group $g(*)$. The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic parameters, and ψ_g is the between-trial covariance matrix for exchangeability group $g = 1, \ldots, \langle G \rangle$. Covariance matrix ψ_g is defined by the standard deviations (t_{g1}, t_{g2}), and correlation r (a common value for r is used across all groups). The parameters t_{g1} and t_{g2} quantify the degree of between trial heterogeneity for exchangeability group g. With different prior distributions for the parameter sets $\left(t_{g1}, t_{g2}\right)$ it is possible to allow for differential discounting for the historical strata. In this way the quality and relevance of historical data can be accounted for in the meta-analysis. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for t_{g1} and t_{g2}, and
- uniform prior for r.

The MAP prior for single-agent model parameters in the new trial, $\left(log(\alpha^*), log(\beta^*)\right)$, is the predictive distribution

$$\left(log(\alpha^*), log(\beta^*)\right) \mid (r_{ds}, n_{ds} : s = 1, \ldots, \langle S \rangle)$$

Since the predictive distribution is not available analytically, the Markov chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using Just Another Gibbs Sampler (JAGS) version 4.8.

Single-Agent Encorafenib

Dose-DLT data from the encorafenib IB (Edition 10) from Study CLGX818X2101 as presented in Table 16 are used to derive the prior of the single agent logistic parameters for encorafenib.

Table 16. Historical Dose Limiting Toxicity data from study CLGX818X2101

Encorafenib Dose (mg; QD)	Number of Participants	Number of Participants with DLTs
50	4	0
100	9	1
150	6	0
200	3	0
300	5 (escalation); 14 (expansion)	1(escalation); 2 (expansion)
450	6 (escalation); 27 (expansion)	0 (escalation); 9(expansion)
550	4	1
700	2	2

Weakly informative normal priors are assumed for μ_{1e} and μ_{2e}, with means corresponding to a 50% chance of DLT at encorafenib = 450 mg and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for t_{1e} and t_{2te} are assigned such that (1) their medians correspond to moderate to large between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Table 17).[8]

Table 17. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Encorafenib Model Parameters

Parameter	Prior Distribution
μ_{1e}	N (mean = 0, sd = 2)
μ_{2e}	N (mean = 0, sd = 1)
t_{1e}	log-normal (mean = log (0.50), sd = log (2)/1.96)
t_{2e}	log-normal (mean = log (0.25), sd = log (2)/1.96)
r_e	Uniform (-1,1)

Single-Agent Binimetinib

Dose-DLT data in the binimetinib IB (Edition 16) from studies ARRAY-162-111 and CMEK162X1101 as presented in Table 18 are used to derive the prior of the single agent logistic parameters for binimetinib.

Table 18. Historical Dose Limiting Toxicity Data from Study Array-162-111 and Study CMEK162X1101

Binimetinib dose (mg BID)	Study Array-162-111		Study CMEK162X1101	
	Number of Participants	Number of Participants with DLTs	Number of Participants	Number of Participants with DLTs
30	3	0	6	0
45	43	2	15	2
60	40	2		
80	3	2		

Weakly informative normal priors are assumed for μ_{1b} and μ_{2b}, with means corresponding to a 50% chance of DLT at binimetinib = 45 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. The priors for between-trial heterogeneity parameters are set in the following way:

- Priors for t_{11b} and t_{12b} (ARRAY-162-111) are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

- Priors for t_{21b} and t_{22b} (CMEK162X1101) are assigned such that (1) their medians correspond to large between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

Study ARRAY-162-111 is a Phase 1 study conducted in advanced or metastatic cancer participants the US. Study CMEK162X1101 is a study in Japanese participants with advanced solid tumors whose disease has progressed despite standard therapy or for whom no standard therapy exists. The participant population in Study CMEK162X1101 is less similar to Study B8011011 and hence large between trial heterogeneity is assumed.

Table 19. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Binimetinib Model Parameters

Parameter	Prior Distribution
μ_{1b}	N (mean = 0, sd = 2)
μ_{2b}	N (mean = 0, sd=1)
t_{11b}	log-normal (mean = log (0.25), sd = log (2)/1.96)
t_{12b}	log-normal (mean = log (0.125), sd = log (2)/1.96)
t_{21b}	log-normal (mean = log (1), sd = log (2)/1.96)
t_{22b}	log-normal (mean = log (0.5), sd = log (2)/1.96)
r_b	Uniform (-1,1)

(t_{11b} ,t_{12b}) = the degree of between trial heterogeneity for Study ARRAY-162-111; (t_{21b} ,t_{22b}) = the degree of between-trial heterogeneity for Study CMEK162X1101.

Single Agent PF-06801591

Dose-DLT data from study B8011001 presented in Table 20 are used to derive the prior of the single agent logistic parameters for sasanlimab.

Table 20. Historical Dose Limiting Toxicity data from Study B8011001

Sasanlimab Dose (mg/once per cycle)	Number of Participants	Number of Participants with DLTs
300	15	0

Weakly informative normal priors are assumed for μ_{1p} and μ_{2p}, with means corresponding to a 50% chance of DLT at sasanlimab = 300mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for t_{1p} and t_{2p} are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Table 21).[8]

Table 21. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Sasanlimab Model Parameters

Parameter	Prior Distribution
μ_{1p}	N (mean = 0, sd = 2)
μ_{2p}	N (mean = 0, sd=1)
t_{1p}	log-normal (mean = log (0.25), sd = log (2)/1.96)
t_{2p}	log-normal (mean = log (0.125), sd = log (2)/1.96)
r_p	Uniform (-1,1)

N=normally distributed; sd=standard deviation.

Prior Distribution for the Interaction Parameters

Normal priors for the log-odds multipliers $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are used. The prior for $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses;

η_{12} is normally distributed, with mean -0.198 and standard deviation 0.101 (corresponds to 20% decrease in DLT odds at median and no increase in DLTs at 97.5th percentile)

η_{13} is normally distributed, with mean 0 and standard deviation 0.467 (corresponds to no increase in DLT odds at median and 2.5-fold increase in DLTs at 97.5th percentile)

η_{23} is normally distributed, with mean 0 and standard deviation 0.467 (corresponds to no increase in DLT odds at median and 2.5-fold increase in DLTs at 97.5th percentile)

η_{123} is normally distributed, with mean 0 and standard deviation 0.354 (corresponds to no increase in DLT odds at median and 2-fold increase in DLTs at 97.5th percentile).

η_{12}: 2-way interaction between encorafenib and binimetinib;

η_{13}: 2-way interaction between encorafenib and sasanlimab;

η_{23}: 2-way interaction between binimetinib and sasanlimab;

η_{123}: 3-way interaction among encorafenib, binimetinib, and sasanlimab.

Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 22.

Table 22. Prior Distribution for the Model Parameters

Parameter	Mean	Standard Deviations	Correlation
Encorafenib single agent parameters: BVN MAP Prior			
$(\log(\alpha_1), \log(\beta_1))$	-0.904, 0.268	0.822, 0.630	0.117
Binimetinib single agent parameters: BVN MAP Prior			
$(\log(\alpha_2), \log(\beta_2))$	-2.785, 0.376	0.596, 0.860	-0.330
Sasanlimab single agent parameters: BVN MAP Prior			
$(\log(\alpha_3), \log(\beta_3))$	-3.247, -0.0135	1.165, 1.009	0.00001
Interaction parameters: Normal prior			
η_{12}	-0.198	0.101	
η_{13}	0	0.467	
η_{23}	0	0.467	
η_{123}	0	0.354	

η_{12}: 2-way interaction between encorafenib and binimetinib;
η_{13}: 2-way interaction between encorafenib and sasanlimab;
η_{23}: 2-way interaction between binimetinib and sasanlimab;
η_{123}: 3-way interaction between encorafenib and binimetinib and sasanlimab.

From Table 23, encorafenib = 300 mg (QD), binimetinib = 45 mg (BID), and sasanlimab = 300 mg once per cycle is an acceptable starting dose for this triple combination.

Table 23. Summary of Prior Distribution of DLT Rates for the Triplet Combination of Encorafenib in Combination with Binimetinib and Sasanlimab

Encorafenib (mg QD)	Binimetinib (mg BID)	Prior probabilities that DLT rate is in the interval:			Mean	SD	Quantiles		
		[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
300	30	0.5815	0.3482	0.0704	0.1645	0.101	0.039	0.141	0.424
300	45	0.5176	0.3723	0.1101	0.1829	0.116	0.039	0.155	0.479
450	30	0.4429	0.4072	0.1499	0.2037	0.124	0.043	0.176	0.515
450	45	0.4246	0.3840	0.1915	0.2172	0.141	0.038	0.184	0.570

Sasanlimab dose fixed at 300 mg per cycle.

Hypothetical On-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose that can be used in the next cohort of participants is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future participants, EWOC criteria and maximum amount of escalation allows (100% of current dose). In practice, the dose recommended by the proposed model may be regarded as guidance. The final recommendation will be based on overall safety profile and PK data.

Table 24 shows data scenarios for the triplet combination and the corresponding recommendations for the next dose.

Table 24. Next Dose Recommendation and the Interval probability of Target Toxicity and Overdosing at Next Dose

	Dose Tested (first 2 dose cohorts)			D/N*	Next Dose options			Pr(TT) at ND	Pr(OD) at ND
Scenario	Enco (mg QD)	Bini (mg BID)	Sasanlimab (mg once per cycle)		Enco (mg QD)	Bini (mg BID)	Sasanlimab (mg once per cycle)		
1	300 450	45 45	300 300	0/3 1/3	450 300	45 45	300 300	0.462 0.409	0.124 0.047
2	300 300	45 45	300 300	1/3 0/3	450 300	45 45	300 300	0.449 0.420	0.137 0.056
3	300 300	45 30	300 300	2/3 0/3	300 300	45 30	300 300	0.544 0.541	0.199 0.110
4	300 300	45 45	300 300	1/3 1/3	300 300	45 30	300 300	0.538 0.542	0.177 0.105
5	300 300	45 30	300 300	2/3 1/4	300	30	300	0.597	0.211

*D=number of participants with DLT; N=number of DLT-evaluable participants; ND=next dose; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing

Operating Characteristics

A simulation study is used to illustrate the properties of the dose finding model guided by BLRM. Several example scenarios were investigated and each scenario 1000 trials were simulated, with results summarized below.

Simulation Scenarios

Several scenarios are considered for the triplet (Table 25). Scenario 1 represents the case when the distribution of DLT coincides with prior, i.e., the true DLT probability equals to mean of prior DLT. Scenario 2 represents an over and under dosing. Scenario 3 represents under dosing and target dosing.

Table 25. Combination A: Dose Limiting Toxicity Rate Scenarios (Fixed Sasanlimab Dose 300 mg Once Per Cycle)

Encorafenib (mg; QD)	Binimetinib (mg; BID)			
	30	45	30	45
	Scenario 1. Prior Means		Scenario 2. Under-Dose and Over-Dose	
300	0.164	0.183	0.100	0.183
450	0.204	0.217	0.297	0.484
	Scenario 2. Under-Dose and Target Dose			
300	0.10	0.12		
450	0.201	0.297		

Simulation Details

Simulations were performed using R version 3.6.1 (The R-project for Statistical Computing. https://www.r-project.org/), and JAGS 4.0 to perform the Markov Chain Monte Carlo (MCMC) analyses.

For each scenario, data for 1000 trials were generated, with a cohort size of 3. At any time during the course of dose finding, escalation to doses where the risk of overdose exceeds 25% is not permitted. The 'next dose recommendation' is the dose with maximum probability of overdose among all dose levels that meet the EWOC criteria.

A simulation of dose-escalation is performed using the starting dose of sasanlimab 300 mg, binimetinib 45 mg, and encorafenib 300 mg. CMEK162X2110 doublet data is considered in this exercise. The maximum number of participants per trial was set to 30. Each trial was stopped when the following criteria were met:

- At least 6 participants have been treated at the recommended MTD $\tilde{d}$.
- The dose $\tilde{d}$ satisfies 1 of the following conditions:
- The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, i.e., Pr $(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
- A minimum of 12 participants have been treated in the trial.

The following metrics were assessed in the simulations:

- Percentage of participants receiving dose combination(s) in the target toxicity interval;
- Percentage of participants receiving an overdose;
- Percentage of participants receiving an under dose;
- Probability that recommended MTD at the end of the trial is in the target toxicity interval;
- Probability that recommended MTD is an overdose;
- Probability that recommended MTD is an under dose;
- Percentage of trials stopped without MTD declaration;
- Average sample size.

Simulation Results

Operating characteristics for triplet dose escalation are presented in Table 26. The percentage of trials with a correctly identified MTD ranges from 92.1% to 96.1%. The average sample size was approximately 9 participants for all scenarios.

Table 26. Combination A: Operating Characteristics

Scenarios	Participant allocation (%)			Pr (declare MTD) (%)			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
Prior means	100	0	0	92.1	0	0	8.0	8.5
With under dose and overdose	81.1	18.9	0	92.1	0	0	8.0	8.5
With under dose and target dose	64.0	0	35.9	96.1	0	0	3.9	8.8

Appendix 3. List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase

Abbreviation	Term
ATC	anatomical therapeutic chemical
AUC	area under the curve
BID	twice daily
BLRM	bayesian logistic regression model
BLQ	below the level of quantification
BOR	best overall response
C_{trough}	lowest concentration
C_{max}	maximum concentration
CALICO	corrected calcium and ionized calcium
CI	confidence interval
CR	complete response
CRF	case report form
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DI	dose intensity
DLT	dose limiting toxicity
DN	dose normalized
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EWOC	escalation with overdose control
EOS	end of study
EOT	end of treatment
FAS	Full analysis set
GCP	good clinical practice
HR	heart rate
irAE	immune related adverse event
LLQ	lower limit of quantitation
LPLV	last participant last visit
MAP	meta-analytic-predictive
MedDRA	medical dictionary for regulatory activities
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NA	not applicable
NAb	neutralizing antibody
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer

Abbreviation	Term
ND	not done
NE	not evaluable
NS	no sample
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic
PR	Partial response
PT	preferred term
QD	once daily
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT corrected for heart rate using Fridericia's formula
QTcB	QT corrected for heart rate using Bazett's formula
Q4W	Once every 4 weeks
Q1	first quartile
Q3	third quartile
PRO	patient reported outcomes
RDI	relative dose intensity
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease
SOC	system organ class
TBILI	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time to first occurrence of C_{max}
TTR	time to response
ULN	upper limit of normal
WBC	white blood cell