Title page

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)

Compound: Sasanlimab (PF-06801591)

Regulatory Agency Identifier Number(s)

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Protocol Number: B8011011

Amendment Number: 4

Phase: Phase 1b/Phase 2

Short Title: Umbrella Study of Sasanlimab in Participants with NSCLC

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Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	
Protocol Amendment 1	04 August 2020	
Protocol Amendment 2	07 December 2020	
Protocol Amendment 3	28 April 2021	
Protocol Amendment #4	21 October 2021	• Master protocol exclusion criterion #13 was clarified to indicate HIV testing if required locally (Section 5.2). • For Sub-Study A, added extra information and concomitant therapy caution for BCRP substrates, P-gp substrates, UGT1A1 inducers, and UGT1A1 inhibitors (Sections 10.13 and 12.6.5.1). • Sub-Study A exclusion criterion #19 and Sub-Study B exclusion criterion #17 were updated to clarify that EGFR mutation status must be known, and that only activating mutations are excluded (Sections 12.5.2 and 13.5.2, respectively). • For Sub-Study A, added that blood samples collected at Screening may be used for development of a medical device/diagnostic test for the $BRAF^{V600}$ mutation (Section 12.1 and 12.8.4). • For Sub-Study A and B, added cf DNA blood draw and removed blood draws for specified gene expression (RNA) and specified protein and metabolic research to prioritize exploratory analysis of ctDNA as a biomarker for outcome (Sections 12.1 and 13.1).

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added a Pre-Screening period in the SoA for Sub-Study B to allow extra time for sites to obtain results of local PD-L1 and/or genetic testing that are required for eligibility; a corresponding row for Eligibility Review was also added (Section 13.1). • Added coagulation testing at Cycle 5 in the SoA for Sub-Study B, as it was inadvertently omitted (Section 13.1). • Added newly obtained information for the monotherapy dose-escalation of SEA-TGT from the FIH study (study SGNTGT-001) (Section 13.2.2.3.2). • Added the SEA-TGT doses in Sub-Study B based on new findings from the FIH study (Sections 13.4.1, 13.4.4.1, 13.6). • For Sub-Study B, reduced frequency of troponin clinical laboratory testing from every visit to Screening/C1D1 and when clinically indicated, because routine monitoring of troponin is not indicated for axitinib or approved immune checkpoint inhibitors (Section 13.10.1). • Injectables were removed from the list of combined hormonal birth control methods that are highly effective and user dependent per new Pfizer standard because there are no approved injectable agents in this category (Sections 12.10.2.4 and 13.10.2.4.) • Moved rationale for Protocol Amendments prior to the current amendment to new Section 10.14 in

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		accordance with the new Pfizer template. • Administrative changes were made to improve readability and consistency of structure and wording across the sub-studies and master protocol.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ ECs, and any protocol administrative clarification letters.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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)

Short Title: Umbrella Study of Sasanlimab in Participants with NSCLC

Rationale:
Master Protocol Rationale

The central scientific theme of the master protocol is that NSCLC is a disease that can be controlled by anti-tumor immunity. Agents that target molecular alterations in these tumors with the potential to increase tumor immunogenicity or agents that target specific pathways of immune resistance in the tumor microenvironment may activate anti-tumor immunity. Once anti-tumor immunity is activated, it is expected that immune checkpoints will be induced as a result of normal homeostatic control of the immune system. The PD-1/PD-L1 interaction has emerged as the most important immune checkpoint limiting anti-tumor immunity in humans. Sasanlimab has shown anti-tumor activity in patients with advanced/metastatic NSCLC comparable to other anti-PD-1/PD-L1 inhibitor monoclonal antibodies. Therefore, blockade of PD-1/PD-L1 interactions through sasanlimab-mediated binding to PD-1 will be the backbone therapy for combination with other agents that may have the ability to induce anti-tumor immunity. Such combination therapies have the potential to induce and sustain long-term disease control in this patient population.

The mechanisms by which anti-tumor immunity becomes established include presentation of tumor antigens within tumor draining lymph nodes and expansion of effector T cells that then traffic to tumors and mediate tumor cell killing. Down-modulatory interactions between such T cells and tumor cells can be induced in the presence of inflammatory cytokines at multiple levels either simultaneously or in series. PD-L1 can be induced on non-immune cells, including tumor cells, in the presence of IFN-γ, a key inflammatory cytokine produced by activated T-cells. PD-L1-mediated down-modulation of T cell activity via engagement of PD-1 on the T-cell surface represents a mechanism to restore immune homeostasis in tissues. The inhibition of PD-L1 interaction with PD-1 in tissue distinguishes the mechanism of anti-PD-1/PD-L1 antibodies from other checkpoint inhibitors such as anti-CTLA-4 antibodies, which primarily act in the context of hematopoietic cells expressing CTLA-4 ligands. As such, single-agent anti-PD-1/PD-L1 antibodies are more effective compared with CTLA-4 blocking antibodies in the treatment of NSCLC, supporting the use of a PD-1 blocking antibody (sasanlimab) as the backbone agent to be used in this master protocol.

Patients with advanced/metastatic NSCLC who experience disease progression while on a first-line PD-1/PD-L1-containing therapy represent an increasing unmet need for more effective therapies. Combinations of agents which can address mechanisms of disease progression and increase the potency of anti-tumor responses could lead to greater depth and durability of anti-tumor responses in tumors that are sensitive to PD-1/PD-L1 therapy.

In addition, for tumors that become resistant to PD-1/PD-L1 therapy, there is a need for new agents that can overcome resistance mechanisms, which could then lead to activation or reactivation of anti-tumor immunity. Nonclinical data suggest that once anti-tumor immunity is re-established in such settings that blockade of the PD-1/PD-L1 pathway will still be needed. Therefore, this master protocol will focus on combinations of sasanlimab with molecularly-targeted agents that have the potential to either restore anti-tumor immunity or inhibit mechanisms of resistance to PD-1/PD-L1 therapy.

The scientific rationale for each of the agents combined with sasanlimab in this study is based on the potential to stimulate anti-tumor immunity and/or increase tumor susceptibility to immune attack. Each sub-study will be comprised of a Phase 1b component to evaluate initial safety and a Phase 2 component to evaluate anti-tumor activity and additional safety. It is initially anticipated that 5 combinations will be explored in this umbrella protocol to provide scientific focus (Figure 1). It is also anticipated that data from this study may be used to inform the design of additional clinical trials.

Participant subgroups will be prioritized for treatment with a given combination based on available data regarding the ability of the combination to prevent, bypass, or reverse resistance to PD-1/PD-L1 therapy. Prospective biomarker testing will be employed in settings where safety and efficacy are known to be contingent on a particular biomarker test result. In settings where the relationships between safety, efficacy, and biomarker test results are either unknown or may be different from the relationships observed for the single-agent components, enrollment may not be based on a test result but retrospective analysis will be used to assess the level of heterogeneity in biomarker-defined subgroups. If such retrospective analysis suggests that the target benefit is only seen in a defined subpopulation, then enrollment into future cohorts could be based on prospective confirmation that participants are members of that subpopulation. These new cohorts will be included in the study via protocol amendment. Control arms may be included within sub-studies to this master study and may be applied to specific treatment settings, where an understanding of the contribution of the individual components of a higher order combination is needed.

Please refer to the sub-study appendices for the rationale of each sub-study.

Objectives and Endpoints

Please refer to the sub-study appendices for the objectives and endpoints of each sub-study.

Estimands

Please refer to the sub-study appendices for the rationale of each sub-study.

Overall 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 as defined in Section 7.1.

The combination arms will be assessed individually in 2 parts:

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

Phase 1b Design:

The sasanlimab dose will remain fixed (at either 300 mg SC Q4W or CCI) for all cohorts in the Phase 1b part of each sub-study.

Guidance for the Phase 1b dosing (dose level to be evaluated in the next cohort) and enrollment decisions (number of participants to be enrolled in the next cohort) will be based on methods described in the appendix for each sub-study.

Phase 2 Design:

Once the Phase 1b is completed for a sub-study and the combination RP2D has been determined, Phase 2 for the sub-study may be initiated to further evaluate the safety and anti-tumor activity. The Phase 2 design will be detailed in the appendix for the respective sub-study.

Number of Participants:
Approximately 375 participants are expected to be assigned to study intervention based on eligibility, assuming the initial plan that 5 combinations will be explored in the umbrella study; refer to the respective sub-study appendix for the sample size determination for each sub-study.

Intervention Groups and Duration:
Study Interventions:

Sasanlimab SC (either 300 mg Q4W or CCI) will be administered in all sub-studies and additional agents will be administered as described in the respective sub-study appendices.

Phase 2 Dose Levels:

RP2D/MTD of sasanlimab + other study drugs

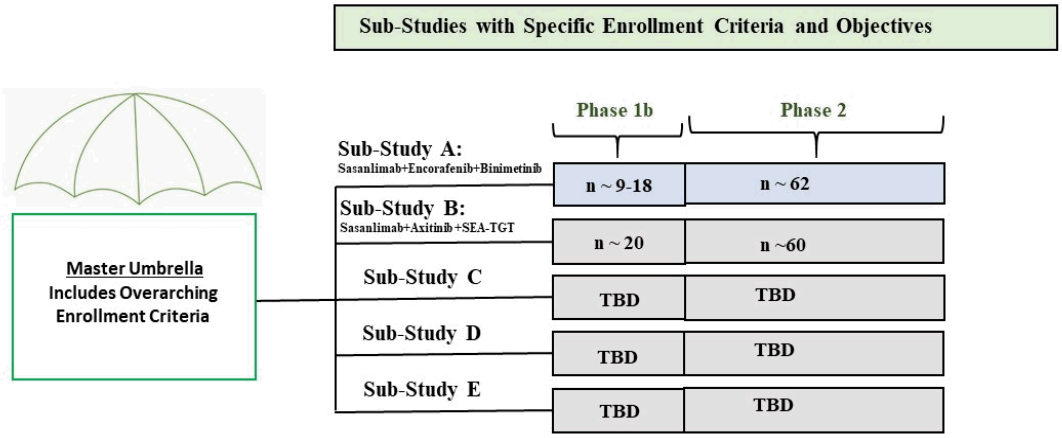
Data Monitoring Committee:
No

Statistical Methods:
The statistical methods will be specified in the respective sub-study appendices.

1.2. Schema

In Sub-Study A, the target population will be participants who have $BRAF^{V600E}$ mutations and the investigational products administered will be sasanlimab, encorafenib, and binimetinib as a triplet therapy. In Sub-Study B, the target population in Phase 2 will be participants without oncogene drivers who have PD-L1- positive tumors (TPS ≥ 1%), and are either treatment-naïve or whose disease has progressed on prior immune checkpoint inhibitor-containing therapy; the investigational products administered will be sasanlimab, axitinib, and SEA-TGT as a triplet therapy.

Figure 1 Master Protocol Study Schematic



1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures.

Refer to the SoA of Sub-Study A in Section 12.1 and the SoA of Sub-Study B in Section 13.1.

2. INTRODUCTION

Study B8011011 is a master protocol for the treatment of participants with locally advanced/metastatic (Stage IIIB-IV) NSCLC, incorporating an anti-PD-1 mAb (sasanlimab, also known as PF-06801591) as the backbone therapy for combinations with different molecularly targeted agents. B8011011 is primarily designed as an exploratory study.

Sasanlimab is a clinically active, humanized, hinge region stabilized immunoglobulin G4 mAb specific for human PD-1 that can selectively bind to human PD-1 and block the interaction between PD-1 and PD-L1/PD-L2.[1] First-in-human studies of sasanlimab show that it has the ability to be administered via SC administration. The convenience of administration coupled with a low rate of injection-related reactions may provide a significant benefit to participants, especially when combined with other anti-cancer agents.[1-4]

The use of PD-1 blocking antibodies alone or in combination with chemotherapy has become a standard-of-care first-line therapy for locally advanced/metastatic NSCLC, with response rates approaching 50%.[2] However, the mPFS of 7.1 months for single-agent pembrolizumab in patients with ≥50% tumor PD-L1 expression[3] and the mPFS of 8.8 months in a broader population of patients treated with chemotherapy/pembrolizumab[2] indicates that the majority of patients will experience disease progression and require a subsequent therapy within their first year of treatment. For patients who experience disease progression on chemotherapy-containing regimens in the first-line setting, the prognosis remains poor for salvage chemotherapy with a mPFS of 4.0 months and an mOS of 8.5 months.[5] In this resistant/refractory setting, single-agent PD-1/PD-L1 inhibitory agents are not therapeutically effective. Therefore, there is an unmet need for more effective therapies for locally advanced/metastatic NSCLC, especially after disease progression on PD-1/PD-L1 inhibitor-containing therapies, where there are limited effective treatment options.

In addition, patients with NSCLC treated with targeted agents will frequently develop resistance to the agents. In settings where there is evidence that the targeted agents trigger an anti-tumor immune response and/or settings where a tumor molecular alteration is associated with active anti-tumor immunity, increased clinical benefit might be experienced by combining tumor-targeted agents with a PD-1 agent, such as sasanlimab.[5]

Combinations of sasanlimab, as a backbone therapy, with new agents will be included in the protocol as sub-studies within appendices. The sub-studies will include the key protocol elements based on the chosen clinical setting, including objectives and endpoints.

2.1. Study Rationale

The central scientific theme of the master protocol is that NSCLC is a disease that can be controlled by anti-tumor immunity. Agents that target molecular alterations in these tumors with the potential to increase tumor immunogenicity or agents that target specific pathways of immune resistance in the tumor microenvironment may activate anti-tumor immunity. Once anti-tumor immunity is activated, it is expected that immune checkpoints will be induced as a result of normal homeostatic control of the immune system. The PD-1/PD-L1 interaction has emerged as the most important immune checkpoint limiting anti-tumor

immunity in humans. Sasanlimab has shown anti-tumor activity in patients with advanced/metastatic NSCLC comparable to other anti-PD-1/PD-L1 inhibitor monoclonal antibodies. Therefore, blockade of PD-1/PD-L1 interactions through sasanlimab-mediated binding to PD-1 will be the backbone therapy for combination with other agents that may have the ability to induce anti-tumor immunity. Such combination therapies have the potential to induce and sustain long-term disease control in this patient population.

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2.2. Background

NSCLC is a disease which is responsive to immune-checkpoint inhibition. In the first-line advanced NSCLC setting, PD-1/PD-L1 inhibitors as single agents are effective in tumors with strong anti-tumor T cell activity which has been down-modulated by tumor-associated PD-L1 expression. High PD-L1 expression is observed in approximately 50% of advanced NSCLC PD-L1-positive cases. For the majority of patients with NSCLC, the use of PD-1/PD-L1 inhibitors as single agents is insufficient to control disease progression.[3]

For patients with advanced NSCLC in the first-line setting, combinations of PD-1/PD-L1 agents with chemotherapy are the most common standard-of-care regimens for those patients who can tolerate chemotherapy and who do not have known targetable aberrations. Upon progression, patients treated with chemotherapy/PD-1/PD-L1 combinations have limited effective treatment options and may be treated with other chemotherapy-containing regimens, which are not highly effective in providing participants with long-term benefit and for docetaxel, the product label contains a black-box warning for severe toxicities.[5-7]

Mechanisms of resistance to PD-1/PD-L1 therapies have been proposed to include β2-microglobulin/MHC Class I down-modulation, insufficient amount of tumor antigens recognizable by T cells, and upregulation of alternative immune suppressive mechanisms (eg, TGFβ pathway upregulation, alternative immune checkpoints, PTEN loss).[8-10]

Combinations of targeted therapies having the capability of stimulating anti-tumor immunity with PD-1/PD-L1 agents have shown improved clinical activity compared with targeted agents alone. Examples include triplet combinations that show activity in patients with metastatic melanoma. Triplet combinations of PD-1/PD-L1 inhibitors with a BRAF inhibitor and MEK inhibitor have shown activity, including a) pembrolizumab with dabrafenib/trametinib or b) atezolizumab with vemurafenib/cobimetinib. In these clinical studies, the addition of the PD-1/PD-L1 inhibitor resulted in an improvement in the durability of responses and trends toward improvement in PFS and OS. ORR was comparable between the targeted agents alone and the triplets.[11,12]

Combinations of sasanlimab with targeted therapy are designed to leverage the relatively rapid reduction in tumor burden possible with targeted therapy and the relatively prolonged tumor control produced by an effective immune response. This hypothesis predicts that the

effect of the targeted therapy will be reflected in the ORR, whereas the effect of sasanlimab will be manifest as extensions of DR, PFS, and OS.

It has been observed in multiple clinical trials of a PD-1/PD-L1 agent with other therapies in NSCLC that due to the kinetics of immune-associated anti-tumor activity, neither the ORR nor mPFS are reliable predictors of OS. In fact, what has been observed with these combinations is that a greater durability of disease control in the intent-to-treat patient population and high maximum depth of the anti-tumor response correlates with an improvement in OS.[13] Accordingly, durable response will be either a primary endpoint or co-primary endpoint with OR, depending on the design of each sub-study.

To summarize, the central goal of this study is to identify combinations that lead to improved anti-tumor activity by activating and sustaining anti-tumor immunity.

2.2.1. Nonclinical Overview

2.2.1.1. Nonclinical Pharmacology

Results from sasanlimab nonclinical pharmacology studies are consistent with the expected effects of blocking the PD-1 pathway and demonstrate the potential to enhance tumor immuno-surveillance and anti-tumor immune responses.

Sasanlimab binds to human PD-1 with high affinity to both recombinant PD-1 protein and cell surface expressed PD-1. Binding affinity to cynomolgus monkey PD-1 was similar to human PD-1. The ability of sasanlimab to block the PD-1 pathway, as measured on primary human and primary cynomolgus monkey T cells, was shown by increased T cell proliferation and cytokine secretion in both of these systems.

See Section 5.1 of the sasanlimab (PF-06801591) IB[14] for detailed information on in vitro and in vivo nonclinical studies.

2.2.1.2. Nonclinical Pharmacokinetics and Metabolism

Single- and repeat-dose PK were assessed after IV and SC dosing of sasanlimab in cynomolgus monkeys. In the GLP toxicity studies, systemic exposure was higher with increasing dose after repeat dosing, and there were no sex-related differences observed in exposure. ADA was observed after repeat IV dosing in monkeys.

Sasanlimab has been shown to induce cytokine production (IFNγ, TNFα, IL-2). However, cytokine-mediated drug interactions observed in the clinic for other anti-PD-1 agents have been modest, resulting in less than 2-fold changes in the exposure of a co-administered small molecule drug.

See Section 5.2 of the sasanlimab (PF-06801591) IB[14] for detailed information on nonclinical studies.

2.2.1.3. Nonclinical Safety

The nonclinical safety profile of sasanlimab has been well-characterized in repeat-dose toxicity studies in cynomolgus monkeys up to 1 month in duration. The IV and SC routes of exposure were assessed as these are the intended routes of administration in initial clinical studies.

In repeat-dose toxicity studies up to 1-month duration in which sasanlimab was administered via the IV or SC routes, no direct target organ toxicities were observed. The key changes associated with sasanlimab treatment of cynomolgus monkeys was minimal to mild mononuclear cellular infiltration of various tissues that persisted and were likely a result of prolonged exposure to sasanlimab throughout the entire recovery phase. These findings are both consistent with expected pharmacology, and previously described in monkey toxicity studies with similar compounds targeting the PD-1 receptor.

See Section 5.3 of the sasanlimab (PF-06801591) IB[14] for detailed information regarding nonclinical toxicology studies.

2.2.2. Clinical Overview

Sasanlimab is being evaluated as a single-agent in Study B8011001 (146 participants with locally advanced or metastatic melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, sarcoma, NSCLC, UC, or other solid tumors); as a single-agent in Study B8011007 (8 participants with advanced malignancies); and in combination with BCG in Study B8011006 (20 participants with high risk non muscle invasive bladder cancer).[14]

Anti-tumor activity of single-agent sasanlimab has been demonstrated in Study B8011001. As of the data cutoff of 01 November 2019, efficacy has been evaluated in 67 participants with NSCLC and 38 participants with UC who were administered sasanlimab 300 mg SC Q4W. The ORR (95% Exact CI) was 20.9% (11.9%-32.6%) in the NSCLC cohort and 21.1% (9.6%-37.3%) in the UC cohort. Median (range) duration of partial response was 230 days (57-445 days) in the NSCLC cohort and 183 days (23-371 days) in the UC cohort.[15]

A total of 60 of 106 participants who were administered sasanlimab 300 mg SC experienced at least 1 treatment-related AE. Most commonly (>5%) reported treatment-related AEs were hyperthyroidism (10.4%), pruritus (7.5%), lipase increased (6.6%), and ALT increased, AST increased, amylase increased, hypothyroidism, rash, and anemia (5.7% each).[15]

Sixteen (15.1%) participants reported ≥ Grade 3 treatment related AEs. Grade 3 treatment-related AEs included lipase increased, amylase increased, and blood alkaline phosphatase increased (1.9% each); decreased appetite, hypermagnesemia, pneumonitis, ageusia, anosmia, jaundice, blood potassium increased, transaminases increased, lymphocyte count decreased, asthenia, fatigue, cognitive disorder, and hypotension (0.9% each). Grade 4 treatment-related AEs included lipase increased, neutrophil count decreased, and white blood cell count decreased (0.9% each). Grade 5 treatment-related AE included arrhythmia (n = 1, 0.9%).[14]

Injection site reactions were infrequent, occurring in <5% of patients. Because monoclonal antibodies may cause reactions such as pain or erythema at the injection site, local tolerability to sasanlimab injections will be assessed. The irAE profile of sasanlimab is mostly consistent with the known safety profile of anti-PD-1 treatment. Treatment-related irAEs commonly identified for sasanlimab include hypothyroidism, hyperthyroidism, and pneumonitis; these have been categorized as ADRs for sasanlimab.

Detailed safety information from clinical studies, as well as nonclinical information, can be found in the sasanlimab (PF-06801591) IB.[14]

Please see Section 12.2.2.1 for a discussion of the clinical overview of investigational products used in combination with sasanlimab in Sub-study A, and Section 13.2.2.3 for agents used in Sub-Study B.

2.3. Benefit/Risk Assessment

Based on data from Study B8011001, there is significant clinical benefit in terms of OR and disease control for participants with advanced/metastatic solid tumors treated with single-agent sasanlimab. These results are consistent with the ORR and DCR in the same tumor types reported for other agents of the same class. Sasanlimab is well tolerated and with a low frequency of treatment-related SAEs.

The benefit risk relationship has been carefully considered in the planning of this study.

Sasanlimab administered at 300 mg SC every 4 weeks has been evaluated in the Phase 1 Study B8011001 in participants with advanced solid tumors as described in Section 2.2.2. The clinical safety data available to date with single-agent sasanlimab suggest an acceptable safety profile with most of the observed AEs in line with those expected in patients with advanced solid tumors or with similar class effects of mAbs blocking the PD-1/PD-L1 axis. Immune-related AEs have been identified as important risks for sasanlimab and risk mitigation measures have been implemented in all ongoing clinical studies, including this study. These measures include guidelines for treatment interruption and discontinuation in case of toxicities, and guidelines for steroid treatment implementation. In the same study sasanlimab has shown evidence of clinical activity aligned to other anti-PD-1/PD-L1 single agents in participants with advanced/metastatic NSCLC.

The fact that PD-1 antagonists are known to be combinable with many other agents is also important to consider. There are exceptional cases where combinations were not tolerated and combinations with agents of the same class will not be conducted in this study. Agents combined with sasanlimab will have a single-agent MTD and/or a RP2D determined in other studies as a basis for the design of the Phase 1b safety cohorts in this study. A safe dose level for each combination will be determined in Phase 1b of this study before proceeding to a Phase 2 expansion cohort.

Based on the above considerations, the benefit/risk assessment for the initiation of Phase 1b safety cohorts for combinations with other agents is favorable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sasanlimab may be found in the IB,[14] which is the SRSD for sasanlimab for this study.

For the benefit/risk assessment of sasanlimab in combination with the targeted agents, see the respective sub-studies (Section 12.2.3 for Sub-Study A; Section 13.2.3 for Sub-Study B).

3. OBJECTIVES AND ENDPOINTS

For sub-study specific objectives and endpoints, refer to each respective sub-study appendix. For Sub-Study A, refer to Section 12.3; for Sub-Study B, refer to Section 13.3.

4. STUDY DESIGN

4.1. Overall Design

The sub-study design specific details are further described in Section 12.4 (for Sub-Study A) and in Section 13.4 (for Sub-Study B).

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 this master protocol. Each sub-study will specify the treatment setting. Participants will receive study drugs until permanent treatment discontinuation criteria are met as defined in Section 7.1.

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Phase 1b Design:

The sasanlimab dose will remain fixed (at either 300 mg SC Q4W or CCI) for all cohorts in the Phase 1b part of each sub-study.

Guidance for the Phase 1b dosing (dose level to be evaluated in the next cohort) and enrollment decisions (number of participants to be enrolled in the next cohort) will be based on methods described in the appendix for each sub-study.

Phase 2 Design:

Once the Phase 1b is completed for a sub-study and the combination RP2D has been determined, Phase 2 for the sub-study may be initiated to further evaluate the safety and

anti-tumor activity. The Phase 2 design will be detailed in the appendix for the respective sub-study (see Section 12.4.2 for sasanlimab in combination with encorafenib and binimetinib and Section 13.4.2 for sasanlimab in combination with axitinib and SEA-TGT).

For Regulatory, Ethical, and Study Oversight Considerations, refer to Appendix 1: Regulatory, Ethical, and Study Oversight Considerations (Section 10.1).

4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the master protocol study rationale.

See the sub-study appendices for the rationales supporting individual combinations.

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

4.3.1. Starting Dose for Phase 1b

Sasanlimab will be given subcutaneously at either 300 mg Q4W or CCI [redacted]. The starting dose for sasanlimab and the combination agents is specified in the respective sub-study appendices.

The sasanlimab dose of 300 mg SC Q4W was selected with considerations of the nonclinical safety data of sasanlimab and the clinical safety and tolerability data from the IV and SC administration cohorts in Study B8011001, along with considerations related to injection volume feasibility of the current formulation.

The sasanlimab dose CCI [redacted] was selected for sub-studies in which the combination product is dosed on a 3-week cycle. The dose of CCI [redacted] yields the same dose intensity as that of 300 mg SC Q4W. It is expected that a similar AUC and a smaller C_{max}/C_{min} fluctuation of sasanlimab will be achieved at steady state after CCI [redacted] dosing compared with 300 mg SC Q4W dosing.

4.3.2. Criteria for Dose Escalation/De-Escalation

The criteria for dose escalation/de-escalation will be specified for each combination in the respective appendix. For the Sub-Study A combination, refer to Section 12.4.4.2; for the Sub-Study B combination, refer to Section 13.4.4.2.

4.3.3. Dose Limiting Toxicity (DLT) Definition

The DLT observation period will be specified for each sub-study. For Phase 1b, any of the following AEs occurring during the DLT observation period which are attributable to 1 or more of the study interventions in the combination will be classified as DLTs.

Hematologic:

1. Grade 4 neutropenia (ANC <500/mm^3 or <0.5 × 10^9/L).

2. Febrile neutropenia, defined as ANC <1000/mm^3 with a single temperature of >38.3°C (>101°F) or a sustained temperature of ≥38°C (≥100.4°F) for more than 1 hour.

3. Neutropenic infection (ANC <1,000/mm^3 or <1.0 x 10^9/L, and Grade >3 infection).

4. Grade 3 thrombocytopenia (platelet count <50,000-25,000/mm^3 or <50.0-25.0 × 10^9/L) with bleeding.

5. Grade 4 thrombocytopenia (platelet count <25,000/mm^3 or <25.0 x 10^9/L).

6. Grade 4 anemia (Life-threatening consequences; urgent intervention indicated).

Non-Hematologic:

7. Any Grade ≥3 toxicity, except for any of the following:

    a. Transient (≤24 hours) Grade 3 fatigue, local reactions, or headache that resolves to Grade ≤1 or baseline status
    b. Grade 3 nausea and vomiting controlled by optimal medical therapy within 72 hours;
    c. Grade 3 hypertension controlled by medical therapy
    d. Grade 3 diarrhea that improves to Grade ≤2 within 72 hours after medical management has been initiated
    e. Grade 3 skin toxicity that resolves to Grade ≤1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated
    f. Grade 3 endocrinopathies controlled with medical therapy
    g. Tumors flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor

8. Non-hematologic Grade 3 laboratory abnormality if medical intervention or hospitalization is required, or any Grade 4 lab abnormality.

9. ALT or AST >3 × ULN (if normal at baseline) or >3 × ULN and doubling the baseline (if > ULN at baseline) and associated with total bilirubin >2 × ULN; or ALT/ AST >5 × ULN; or total bilirubin >3 × ULN.

Non-Adherence to Treatment Schedule:

10. Failure to receive at least 75% of the planned doses of each of the investigational products during the DLT observation period due to treatment-related toxicities

Other criteria:

11. An AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT after consultation between sponsor and investigator, based on the emerging safety profile.

The following AEs will not be considered as DLTs:

Single laboratory test values out of normal range that do not have any clinical correlate and resolve to Grade ≤1 or baseline within 7 days with adequate medical management are not to be considered DLTs.

Grade 3 IRR, allergic reaction or anaphylaxis will not be considered as DLTs but may be a reason for permanent treatment discontinuation and will be reviewed with the sponsor.

4.3.4. Maximum Tolerated Dose (MTD) Definition

The maximum tolerated dose will be defined for each sub-study dependent on the dose finding method.

4.3.5. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose level of the combination that will be chosen for further development and evaluation in Phase 2.

The RP2D may be determined based on other safety, clinical activity, PK, and pharmacodynamic data and may be the MTD, a dose below the MTD or highest studied dose if the MTD is not reached at the highest studied dose.

4.4. End of Study Definition

The end of the study is defined as the date of study completion for the last participant in the trial globally, at sponsor discretion if the data support ending the study, or 3 years after first dose of the last participant, whichever is earlier.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this master protocol and sub-studies.

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

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent

document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data or other site documentation.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following master protocol criteria apply, as well as sub-study specific inclusion criteria provided in the respective sub-study appendices:

Phase 1b and Phase 2 For All Sub-Studies:

Informed Consent:

1. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with requirements and restrictions listed in the ICD and in this protocol.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

Age and Sex:

3. Male or female participants age ≥18 years at Screening (except in Japan, where participants must be ≥20 years).

4. Male and female participants must agree to contraceptive use according to reproductive criteria described in Appendix 4.

5. Female participants of childbearing potential must have negative serum pregnancy or urine pregnancy test at Screening.

Type of Participant and Disease Characteristics:

6. Documented histologically or cytologically confirmed locally advanced/metastatic (Stage IIIB-IV) NSCLC, per AJCC/ International Union for Cancer Control TNM system, 7th edition.[16] For Stage IIIB disease relapse during treatment or within 6 months following adjuvant therapy will be considered metastatic disease. In addition, for Stage IIIB, must not be amenable for definitive therapy (eg, surgery or chemoradiation).

7. At least 1 measurable lesion per RECIST v1.1 at Screening.

8. ECOG Performance Status 0 or 1.

9. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1, unless otherwise specified.

10. Life expectancy ≥3 months as assessed by the investigator for previously treated participants or ≥12 months for first-line untreated participants.

11. Adequate bone marrow function (without hematopoietic growth factor or transfusion support within 14 days prior to first dose of study intervention), including:

    a. Absolute neutrophil count ≥1500/mm^3 or ≥1.5 × 10^9/L;

    b. Platelets ≥100,000/mm^3 or ≥100 × 10^9/L;

    c. Hemoglobin ≥9 g/dL (may have been transfused).

12. Adequate renal function, defined by:

    Estimated creatinine clearance ≥30 mL/min according to the Cockcroft-Gault formula or by 24-hour urine collection for creatinine clearance, or according to local institutional standard method.

13. Adequate liver function, including:

    a. Total serum bilirubin ≤1.5 × ULN unless the participant has documented Gilbert syndrome;

    b. AST and ALT ≤2.5 × ULN; ≤5.0 × ULN if there is liver involvement by the tumor;

    c. Alkaline phosphatase ≤2.5 × ULN (≤5 × ULN in case of bone metastasis).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following master protocol criteria apply, as well as sub-study specific exclusion criteria provided in the respective sub-study appendices:

Medical Conditions:

1. Active or prior autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Participants with diabetes type I, vitiligo, psoriasis, or hypothyroid or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

2. Previous Grade ≥3 irAE; or unresolved irAEs prior to first dose of study intervention.

3. Active non-infectious pneumonitis, pulmonary fibrosis, or known history of immune-mediated pneumonitis.

4. Active infection requiring systemic therapy.

5. Clinically significant cardiovascular diseases, including any of the following:

   a) History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft, coronary angioplasty or stenting) ≤6 months prior to start of study treatment;

   b) Congestive heart failure requiring treatment (New York Heart Association Class ≥2);

   c) Uncontrolled hypertension defined as persistent systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100 mmHg despite optimal therapy;

   d) History or presence of clinically significant or uncontrolled sustained cardiac arrhythmias (including uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);

   e) History of thromboembolic or cerebrovascular events ≤3 months prior to the first dose of study treatment. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (ie, massive or sub-massive) deep vein thrombosis or pulmonary emboli.
   Note: Participants with either deep vein thrombosis or pulmonary emboli that do not result in hemodynamic instability are allowed to enroll as long as they are stable, asymptomatic and on stable anticoagulants for at least 2 weeks.
   Note: Participants with thromboembolic events related to indwelling catheters or other procedures may be enrolled.

6. Other malignancy within 2 years prior to the first dose of study intervention, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason 6 or below) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration) or other concurrent malignancy investigator feels has a very low likelihood to become metastatic.

7. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis.

8. Symptomatic brain metastasis: participants previously treated for this condition or untreated with brain metastases <10 mm without associated edema, who are asymptomatic in the absence of corticosteroid therapy are allowed.

9. Leptomeningeal disease.

10. Known history of acute or chronic pancreatitis.

11. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

12. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

13. Participants with active, uncontrolled bacterial, fungal, or viral infection, including HBV, HCV, or known HIV infection. If HIV infection status is unknown, testing for HIV must be performed at sites where mandated locally.

Prior/Concomitant Therapy:

14. Live attenuated vaccines within 4 weeks prior to first dose of study intervention and while on study treatment.

15. Major surgery or received radiation therapy within 2 weeks prior to first dose of study intervention.

Other Exclusions:

16. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partners from the permitted list of contraception methods (see the respective sub-study appendix) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use protocol-specified contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

Contraception details will not be entered in a CRF.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number .

6. STUDY INTERVENTION

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

Sasanlimab is 1 of the study interventions and will be provided in a prefilled syringe or vial for SC injection. The prefilled syringe is a medical device. Additional study interventions will be detailed in their respective sub-study appendices.

6.1. Study Intervention(s) Administered

Sasanlimab will be administered in all sub-studies and additional agents will be administered as described in the respective appendices. Study intervention of sasanlimab is administered as shown in Table 1.

Table 1. Study Intervention Sasanlimab

Intervention Name	sasanlimab
Type	Biologic Product
Dose Formulation	Solution for Injection
Unit Dose Strength(s)	150 mg/mL, 2 mL (300 mg total) prefilled syringe Or 50 mg/mL, 2 mL (100 mg total) vial
Dosage Level(s)	300 mg Q4W or CCI [redacted]
Route of Administration	Subcutaneous
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor (manufactured by Pfizer)
Packaging and Labeling	Study intervention will be provided in either a prefilled syringe or vials for the 300 mg dose; study intervention will be provided in vials for the CCI [redacted]. Each prefilled syringe or vial will be labeled as required per country requirement.

6.1.1. Administration of Sasanlimab

Qualified and trained investigator site personnel will administer sasanlimab at a fixed dose of 300 mg once every 4 weeks CCI [redacted] by SC injection to the abdomen of participants ; see the respective sub-study appendix for the dose of sasanlimab to be administered in each sub-study. The 300 mg Q4W dose will be administered by either 1 prefilled syringe or, if provided in vials, 3 SC injections will be administered. For the CCI [redacted] dose, vials will be provided and 3 SC injections will be administered; the maximum volume per injection should be 2 mL. See Section 8.2.7 for local site injection tolerability assessment.

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

Study staff should refer to the IP Manual for specific instructions on the preparation, handling, and administration of the study intervention.

A cycle is defined as the time from Day 1 dose to the next Day 1 dose. Participants will receive a single dose of sasanlimab on Day 1 of each cycle. Each participant may receive sasanlimab until completion of study treatment, progression of disease, unacceptable toxicity, withdrawal of consent, participant no longer willing to participate in trial, end of study or study termination.

6.1.2. Medical Devices

This section is applicable only to sub-studies using the pre-filled syringe for sasanlimab administration, not for sub-studies using the vial formulation.

1. The medical device used to deliver sasanlimab is a prefilled syringe.

2. Instructions for medical device use are provided in the investigational product manual.

3. Medical device deficiencies (including malfunction, use error, and inadequate labeling) must be detected, documented, and reported by the investigator throughout the clinical investigation and appropriately managed by the sponsor (see Section 8.3.9).

6.2. Preparation/Handling/Storage/Accountability of All IP

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention, when applicable.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. When applicable, all study interventions that are taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing of All IP

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

6.3. Measures to Minimize Bias: Randomization and Blinding

Refer to the respective sub-study (See Section 12.6.3 for Sub-Study A and Section 13.6.3 for Sub-Study B).

6.3.1. Allocation to Study Intervention

Once a participant has signed consent, the site staff will complete registration in the IRT system. The IRT will assign a participant identification number and supply this number to the site. The participant identification number will be used on all study-related documentation at the site.

Allocation of participants to treatment groups will proceed using an IRT system (IWR). Specification of the dose level for each participant in Phase 1b will also be provided by the IRT. Allocation of participants will be approved only after all entry criteria have been reviewed by the sponsor, and no earlier than 3 days prior to C1D1 dosing.

The site personnel (study coordinator or specified designee) will be required to have an active or valid account and password with the IRT system, enter or select information including but not limited to the protocol number, specific protocol entrance criteria indicated in the system and the screening number. The site personnel will then be provided with, at a minimum, a treatment assignment, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, allocation number and DU or container number assigned. The confirmation report must be stored in the site's files. Study intervention will be dispensed at the study visits as summarized in the SoA. Returned study intervention must not be redispensed to the participants.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

For additional details on the allocation of study intervention, refer to the respective sub-study appendix.

6.4. Study Intervention Compliance

Sasanlimab will be administered by the appropriately designated study staff at the investigational site and compliance will be documented. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

For study interventions that are administered at home as described in each sub-study, participant compliance with study intervention will be assessed at each visit. In order to document and assess participant compliance with study interventions administered at home, participants will record each self-administration of study intervention using a diary. Data entered in the diary will be compared with drug accountability done at the site (ie, counting returned capsules/tablets vs dispensed capsules/tablets) prior to dispensing additional study treatment.

When applicable and as instructed in the IP manual, the site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.5. Concomitant Therapy

All prior and concomitant treatments, received by participants from screening and up to 30 days after the last dose of study treatment, or up to the start of new anti-cancer therapy, including supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions) will be recorded on the CRF. Concomitant medications for AEs and SAEs should follow respective guidance for the AE and SAE reporting period.

Prohibited therapies and concomitant therapy instructions during the study are listed in this section and in the sub-study appendices. If there is a clinical indication for 1 of the medications specifically prohibited during the study, discontinuation from the study treatment may be required. Participants may receive other medications that the investigator deems to be medically necessary. The final decision on any supportive therapy rests with the Investigator and/or the participant's primary physician. The decision to continue the participant in the study requires mutual agreement of the investigator, the sponsor and the participant.

Any questions regarding administration of concomitant medications should be directed to the sponsor.

6.5.1. Other Anti-tumor/Anti-cancer or Experimental Treatments

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. No other investigational drugs and devices are permitted while receiving study treatment.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. The participant must have clear measurable disease outside the radiated field.

In view of the current lack of data about the interaction of investigational products with radiotherapy, study treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming study treatment after recovery of any radiotherapy associated signs and symptoms to baseline.

Radiotherapy to a target lesion during the study will result in a subsequent unevaluable responses per RECIST v1.1 (Section 10.9).

6.5.2. Supportive Care

Palliative and supportive care for disease-related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current ASCO guidelines.

6.5.3. Hematopoietic Growth Factors

Granulocyte-colony stimulating factors may be used for treatment-emergent neutropenia as indicated within the current ASCO guidelines.[17] Primary prophylactic use of granulocyte-colony stimulating factors is not permitted.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia. Erythropoietin is not approved in some countries for anemia caused by cancer treatment. For those countries where the indication and dosage of G-CSF compounds may differ from ASCO guidelines, refer to local package insert or follow clinical practice in their countries.

6.5.4. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis is not required. If required for individual participant, the decision to incorporate pre-medication will be made following discussions between the sponsor and the investigator.

6.5.5. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction.

6.5.6. Corticosteroids

Chronic, systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purpose is not permitted. Acute emergency and short-term administration of corticosteroids are allowed. If immune-related AEs occur, immune suppressive treatment should be administered according to local standards or practice. Sasanlimab will not be resumed while a participant is receiving immunosuppressive doses of corticosteroids.

The use of steroids during this trial is restricted as follows:

a) Therapeutic use: for the treatment of infusion-related reactions, short-term treatment of irAEs, and other drug-related AEs, steroids are permitted according to the modalities indicated in the respective toxicity management sub-study appendices.

b) Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.

c) Intranasal, inhaled, topical steroids, eye drops, or local steroid injections (eg, intra-articular injection) are permitted.

Any other use of corticosteroids should be discussed with the sponsor before implementation.

6.5.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and study intervention required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping study intervention is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate study intervention treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

Surgery to a target lesion during the study will result in subsequent unevaluable responses per RECIST v1.1 (Section 10.9).

6.5.8. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with sasanlimab; standard medical supportive care must be provided to manage the AEs.

6.5.9. Proton-Pump Inhibitors

No restrictions unless specified in sub-studies.

6.5.10. Antacids or H2-Receptor Antagonists

No restrictions unless specified in Sub-Studies.

6.5.11. Vaccines Administration

Live attenuated vaccines within 4 weeks prior to the first dose of sasanlimab and through 30 days following the last dose of sasanlimab are not allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally inactivated virus vaccines and are allowed; however intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.

6.6. Dose Modification

Sasanlimab

Every effort should be made to administer study intervention on the planned dose and schedule. In the event of significant toxicity, dosing may be delayed and/or skipped as described below; no dose reductions are permitted for sasanlimab. Dose reductions may be allowed for other study treatments administered in combination with sasanlimab and will be specified in their respective sub-study appendix. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed (and attribution for the combination treatment). Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom. The following treatment modifications will be allowed as described in Table 2 and Section 10.10:

Dose Interruption/Delay: If a participant develops a treatment related AE meeting withhold the treatment criteria, the treatment administration should be immediately stopped and should not be resumed until the criteria to restart treatment are met.

If any treatment-related AE is not resolved by the next scheduled dosing, the dosing should be delayed until the criteria to restart treatment are met.

Missed Dose: The next dosing of sasanlimab may be skipped for the cycle based on persisting toxicity.

Permanent Treatment Discontinuation: If a participant develops a treatment-related AE meeting permanent discontinuation criteria as defined in Section 7.1, all the treatments considered related to the AE should be discontinued. The treatments not considered related to the AE can be continued.

General Treatment Modification Guidelines:

Treatment modifications, delays, interruptions or discontinuations should be assigned to each product based on the causality assessment, when possible.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

All treatment modifications should be based on recommendations described in Table 2 and the respective sub-study appendix, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

All treatment modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Depending on when the AE resolved, a treatment interruption may lead to delay of the initiation of the subsequent cycle.

The treatment modification guidelines for the drugs to be administered in combination with sasanlimab will be specified in the respective sub-study appendices.

Table 2. Sasanlimab Recommended Treatment Modifications for Study Intervention-Related Toxicity (Excluding Immune-Related AEs)

Hematologic toxicities	
Grade 1 and Grade 2	Continue as per schedule.
Anemia Grade ≥3 (hemoglobin <8 g/dL)	Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. Permanently discontinue sasanlimab if anemia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Neutropenia Grade ≥3 (ANC <1000/µL)	Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. Permanently discontinue sasanlimab if neutropenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Thrombocytopenia Grade ≥3 (platelets <50,000/µL)	Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. Permanently discontinue sasanlimab if thrombocytopenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Non-hematologic toxicities	
Grade 1	Continue as per schedule.
Grade 2	First occurrence: continue per schedule. Follow modifications for Grade 3 event if Grade 2 AE is considered intolerable and recurrent based on medical judgment.
Grade 3	Hold sasanlimab. Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. **Exceptions are:** laboratory values that do not have any clinical correlate. For suspected immune-related toxicity follow guidance in Section 10.10.
Grade 4	Permanently discontinue sasanlimab. **Exceptions are**: laboratory values that do not have any clinical correlate. For suspected immune-related toxicity follow guidance in Section 10.10.

6.6.1. Management of Treatment-Related Adverse Events

Since inhibition of PD-1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity as outlined in Section 10.10 for the management of irAEs related to sasanlimab.

For any irAE of any grade, the investigator may consider consulting with the sponsor's medical monitor if deemed necessary.

Treatment of irAEs should follow guidelines set forth in Section 10.10.

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex-mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of administration and may include symptoms such as rash, urticaria, polyarthritis, myalgias, polysynovitis, fever, and if severe, glomerulonephritis.

All participants should be closely observed while receiving sasanlimab. Monitoring for clinical signs of a systemic reaction should continue thereafter for clinical signs of allergic reactions/hypersensitivity.

In case of a hypersensitivity reaction, the participant will be treated symptomatically, with supportive care and further monitoring until the end of the study. Guidance on dose interruptions and potential retreatment is detailed in Table 2.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

See the respective sub-study SoA for data to be collected at the time of study treatment discontinuation (End of Treatment (EOT) visit assessments) and follow-up and for any further evaluations that need to be completed.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;

- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

The discontinuation of study intervention is defined as the discontinuation of all the assigned study drugs.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for survival. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Treatment after Initial Evidence of Radiological Disease Progression

Immunotherapeutic agents, such as sasanlimab, may produce anti-tumor effects by potentiating endogenous cancer specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression after dosing with the investigational product(s), participants may continue to receive investigational products, at the investigator's discretion if the following criteria are met:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression;
- No decline in ECOG performance status;
- Absence of rapid progression of disease by radiographic imaging;
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If the participant is subsequently found to have further disease progression at a subsequent tumor assessment, either radiologically according to RECIST v1.1 or clinically, then treatment with investigational products should be permanently discontinued.

7.1.2. Rechallenge

Retreatment within the study after permanent discontinuation of treatment is not allowed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request.

Reasons for discontinuation from the study may include:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent for disclosure of future information (see Section 7.2.1), no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

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

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

The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study is handled as part of Section 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the respective sub-study SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations and applicable Cycle 1 Day 1 evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the

investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner. Guidance for handling protocol-required tests and procedures in public emergencies is provided in Section 10.12.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

8.1.1. Tumor Response Assessment

RECIST version 1.1 (see Section 10.9) will be applied by the site as the primary measure of tumor assessment and response and as the basis for protocol guidelines related to disease status (eg, discontinuation of study treatment).

Radiological scans of all suspected sites of disease will be performed utilizing the same method and technique throughout the study. Target lesions should demonstrate the participant's baseline tumor burden and will be selected based on size (i.e., lesions with the longest diameter), and suitability for accurate repeat assessment.

The following should be performed at Screening/baseline:

- Chest, abdomen, and pelvis CT or MRI scans are required for all participants at Screening.
- An MRI of the brain is also required for all participants at Screening. A CT scan of the brain, preferably with IV contrast, may be performed if MRI is contraindicated. Additional imaging of anatomical sites (eg, head, neck, etc.) should be performed as applicable based on location of disease sites.
- Bone imaging using bone scan (bone scintigraphy), ^{18}F-FDG-PET, MRI, or other methods considered standard of care locally is required at baseline only if bone metastases are known or suspected outside the body areas scanned using other techniques.
- Radiographic assessments obtained per the participant's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as the Screening/baseline evaluation, if, (1) obtained within 28 days prior to first dose of study treatment, (2) performed using the method requirements (ie, RECIST v. 1.1), (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given participant, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the participant's source notes.

The following should be performed during the study/postbaseline:

- During the study chest, abdomen, and pelvis CT or MRI scans are required for all participants. Additional imaging of anatomical sites (eg, head, neck, etc.) should be performed as applicable based on location of disease sites.

- Subsequent MRIs of the brain will only be performed if there were lesions present at baseline or if new brain metastases are suspected.

- If bone lesions are present at baseline, bone imaging should be performed every 12 weeks for the first year and every 24 weeks thereafter. Bone imaging is also required at the time of confirmation of CR for participants who have bone metastases. Otherwise, bone imaging is required only if new bone metastases are suspected.

- Additional imaging evaluations may be performed at any time if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical examination.

Chest X-ray or ultrasound should not be used for tumor response assessments in this study.

While ^{18}F-FDG-PET scans are not required for this study, sites may perform combined PET/CT scans per their local standard of care, provided the CT is of similar diagnostic quality as CT performed without PET, including the use of oral and IV contrast media. If acquired according to local standard of care ^{18}F-FDG-PET may be relied upon to document PD in accordance with RECIST.

For participants with known CT contrast allergy, a non-contrast CT of the chest with contrast enhanced abdominal and pelvic MRI can be used. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the subsequent tumor assessments. If the imaging technique is changed due to unavoidable circumstances, as assessed by radiologist/investigator, and a comparable measurement of lesion is feasible then the tumor measurement should be reported, otherwise the lesion should be reported as non-evaluable.

CT or MRI scans must be completed before tumor biopsy samples are collected.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at following occasions:

- At timepoints specified in the SoA.

- Whenever disease progression is suspected (eg, symptomatic deterioration).

- After first occurrence of PR or CR is observed according to RECIST v1.1, repeat imaging at least 4 weeks after initial documentation.

- At the time of withdrawal from treatment if not done in the previous 8 weeks and prior response if other than PD.

Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

All participants' files and radiologic images must be available for source verification and for potential peer review. Radiologic images must be made available to a central vendor, if specified in the respective sub-study appendix, for potential central imaging reading.

For participants who did not end treatment due to disease progression, or withdrawal of consent, a tumor assessment will be performed as per SoA, post the EOT visit, until disease progression by RECIST v1.1, or initiation of a new anti-cancer treatment, or end of study, whichever is first.

8.1.2. Tumor Markers

No tumor markers will be collected for efficacy assessment.

8.1.3. Overall Survival

Following completion of the 180-day follow-up period all participants who receive study drug in Phase 2 will be followed for survival status (independent of time of disease progression) and subsequent anti-cancer treatments. The assessment can be conducted by telephone every 12 weeks (±7 days) until death, lost-to-follow-up, study discontinued by sponsor, end of study, or participant withdrawal of consent of study, whichever comes first. If the participant is seen in the clinic during the time window that a scheduled telephone call is to be made to collect survival data, the clinic visit may replace the survival telephone call.

To ensure current and complete survival data is available at the time of final analyses, updated survival status may be requested at any time during the course of the study by the sponsor. Upon sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the respective sub-study SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

Physical examinations will be assessed as per the respective sub-study SoA. The body systems included in the scope of examination will be decided by the treating physician based on the standard of care at the center. The details of the physical examination will not be

recorded on a CRF; however, any abnormalities detected during the physical examination will be reported on the medical history or adverse event CRF as appropriate.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height and weight will also be measured and recorded as per the SoA.

8.2.2. Vital Signs

Temperature, pulse rate, and blood pressure will be assessed as per the SoA. Temperature and pulse rate need not be recorded in the CRF but abnormalities will be recorded on the medical history or AE CRF as appropriate.

Blood pressure and pulse measurements will be assessed in a sitting or supine position preferably with an automated device and should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions and prior to administration of any study drug or other study procedure.

8.2.3. Electrocardiograms

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs as outlined in the SoA. At each time point where triplicate ECG is required, 3 serial 12-lead ECGs will be conducted within approximately 5-10 minutes total time to determine mean QTc (average of triplicates).

For remaining timepoints, single ECG will be collected prior to administration of study drug. If abnormalities are found on a single ECG, then a triplicate should be performed. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection.

Additional ECGs may be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.

If participant experiences a cardiac or neurologic AE (specifically palpitations, syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event.

To ensure safety, if there is finding of QTc prolongation (≥60 msec from the pre-dose baseline, or >500 msec), ECG must be reviewed by qualified personnel at the site as soon as the finding is made, overreading the machine reading and ensuring that the Fridericia correction formula is applied. If manual reading verifies the observation, repeat ECGs should be immediately performed at least 2 times approximately 2 minutes apart. In such cases, when reporting ECG data in CRF, manual reading should be reported. The Fridericia correction formula is:

$QT_CF = QT / RR\ interval^{1/3}$

ECG values of potential clinical concern are listed in Section 10.7.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical safety laboratory tests to be performed and the SOA of each sub-study for the timing and frequency. All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the sub-study SOA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report prior to each dosing, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Section 10.6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

Results from the protocol-specified laboratory assessments that should be recorded in the CRF will be outlined in the CRF Completion Guidelines.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SOA for each sub-study. Home pregnancy tests may be utilized for visits indicated in the SoA for each sub-study, if compliant with local regulatory requirements. The home urine pregnancy testing kit must have a sensitivity of at least 25 mIU/mL. The pregnancy test outcome should be documented in the participant’s source documents/medical records.

Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit prior to the participant’s receiving the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations.

8.2.6. ECOG Performance Status

ECOG Performance Status will be evaluated as outlined in the SOA for each sub-study. Refer to Table 3 for ECOG Performance Status Criteria.

Table 3. ECOG Performance Status

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

Source: Oken M et al, 1982.[18]

8.2.7. Local Site Injection Tolerability Assessment

Assessments to monitor local tolerability to sasanlimab SC injections will be performed as outlined in the respective SoA.

Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported; otherwise details of these assessments will not be recorded on the CRF. When appropriate, at the discretion of the investigator, a participant with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR. If injection site reaction is noted, site tolerability assessments should continue until the symptoms resolve.

8.2.8. 30/60/90/180 Day Follow-Up Visits

The initial safety follow-up visit will be conducted in the clinic 30 days after last dose of study drug. The 60-, 90-, and 180-day follow-up visits will be performed via remote contact (eg, telephone). The investigator may conduct these follow-up visits in clinic if any concerns are noted during the remote contact. Refer to Section 8.1.1 for guidance on tumor assessment during the Follow-up periods. Refer to the respective sub-study SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 8. Device deficiencies are covered in Section 8.3.9.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study related procedure and/or receiving study intervention), through and including a minimum of 90 calendar days after the last administration of the study intervention.

During the long-term follow-up period in this study for survival, only SAEs will be actively elicited and collected after completion of the active collection period described above. The SAEs identified during long-term follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study intervention.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study treatment and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a liveborn baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

See Section 10.7 for ECG findings of concern.

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

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. An AE should still be reported for signs or symptoms due to progression of the malignancy.

8.3.8. Adverse Events of Special Interest

Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Section 10.10.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

Lack of efficacy (see Section 10.3.1) is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

The medical device being provided for use in some sub-studies is the prefilled syringe for SC injection; see the respective sub-study appendices for details on whether the medical device will be included in the sub-study. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device deficiency can be found in Appendix 8.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Sections 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator or site staff will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 8.

8.3.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP Manual.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong administration site, or at the wrong time, or at the wrong dosage strength, or from inadvertent exposure.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- Incorrect study intervention taken by participant.
- Overdosing.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.4. Treatment of Overdose

Administration of any dose of sasanlimab greater than the assigned dose level at any scheduled administration visit will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose for any of the study drugs.

In the event of an overdose, the treating physician should:

1. Provide the appropriate supportive treatment as clinically indicated.

2. Contact the medical monitor within 24 hours.

3. Closely monitor the participant for any signs of toxicity, AEs, and laboratory abnormalities for at least 6 months after the overdose.

4. Obtain a plasma sample for PK analysis with clear documentation of the time it is collected relative to the date of the last dose of study intervention, if requested by the sponsor (determined on a case-by-case basis).

5. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6. Overdose is reportable to Safety only when associated with an SAE.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

Instructions for treatment of overdose for the drugs to be administered in combination with sasanlimab will be specified in the respective sub-study appendices.

8.5. Pharmacokinetics

The PK sampling schedule is specified in the respective appendix for each sub-study and may be modified based on emerging PK data. Additional PK samples may be drawn on discussion with sponsor (ie, to investigate a safety event, etc).

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the source document and CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, participant and sponsor.

PK samples will be analyzed using a validated analytical method.

Details regarding the collection, processing, storage and shipping of the PK blood samples will be provided to the investigator site prior to initiation of the trial. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

As part of understanding the PK of the study interventions, samples may be used for metabolite identification and/or further bioanalytical evaluation, as well as for other internal exploratory purposes. These data may not be included in the Clinical Study Report (CSR).

Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, may be destroyed.

8.5.1. Blood for PK Analysis of Sasanlimab

Blood samples (3-mL whole blood at each time point) will be collected for PK analysis of sasanlimab, as outlined in the respective sub-study SoAs. Refer to the Laboratory Manual for instructions for specific details on collection tubes, processing, and shipping.

8.5.2. Blood for PK Analysis of Combination Target Agents

Blood samples will be collected for PK analysis as described in the respective sub-study SoAs. Refer to the Laboratory Manual for instructions for specific details on collection tubes, processing, and shipping.

8.6. Pharmacodynamics

Exploratory analyses may be performed in response to emerging data on possible interactions between study treatments.

As part of understanding the pharmacodynamics of the investigational product, samples collected in the sub-study may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the CSR.

The pharmacodynamic samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the pharmacodynamic sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may decide whether sample integrity has been compromised.

8.7. Genetics

8.7.1. Specified Genetics

Genetic assessments for all sub-studies will be performed utilizing tumor and blood samples as collected and described in the respective sub-study SoAs.

Biospecimen to confirm eligibility: DNA samples may be analyzed for the purpose of confirming the presence of DNA alterations (eg, $BRAF^{V600E}$) if required for enrollment to the study arm.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant, or the participant's tumor biopsy may be used to confirm the presence

of the DNA alterations. See the Genetics section of the individual sub-studies for additional details of the eligibility assessments.

Baseline tumor biopsy: Whole exome sequencing of participant's tumor biopsy will be performed on qualifying specimens to characterize DNA alterations that may be associated with response to therapy. TCR sequence analysis may be performed on qualifying tumor biopsies to assess associations between tumor-associated TCRs and clinical outcomes.

Blood for cell-free DNA analysis: samples may be analyzed for epigenetic and/or genetic associations with clinical outcomes.

Blood for specified genetic research:

Whole genome sequencing of participants' blood samples collected prior to initiation of study therapy may be performed to confirm somatic vs germline nature of DNA alterations detected in matched tumor samples. Whole genome sequencing of samples may also be performed to characterize epigenetic modifications of DNA. Genetic variation at specific loci (such as FCGR genes) or epigenetic modifications in peripheral blood may also be assessed by targeted assays using PCR or NGS-based methods applied to white blood cells or cell-free DNA.

Blood for TCR analysis: A separate peripheral blood specimen will be collected to monitor the T Cell Receptor repertoire over the first 2 cycles of therapy according to the SoA of each sub-study.

The sequencing methods will not have been validated for diagnostic use to assess predisposition to genetic disease. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for DNA isolation (Prep D1) will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the interventions and NSCLC. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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

8.8. Biomarkers

Biomarker data collected by investigator sites as part of standard clinical practice may be recorded in the CRF. Such data may include but not be limited to PD-L1 status and presence or absence of alterations in genes such as BRAF, EGFR, ALK, ROS1, or KRAS.

Collection of samples for biomarker research is also part of this study. Results from some of the biomarker research may be provided to the investigator.

The following samples for biomarker research will be collected from participants as specified in the respective sub-study SoA:

- If baseline tumor samples are required prior to initiation of study therapy, the tumor collection procedure date should be as close to the start of study therapy as clinically feasible, and not before start of systemic cancer therapy. Tumor samples collected prior to systemic cancer therapy may be acceptable in select cases upon consultation with the sponsor. If a suitable tissue sample is not otherwise available, then an FFPE tissue sample from a de novo biopsy must be obtained during the screening period. The tumor samples should be collected by resection or core needle biopsy; if these options are contraindicated, fine needle aspirates are allowed. Core biopsies should be performed using a minimum 18-gauge needle whenever feasible to preserve tissue integrity for histological and structural assessment. A minimum of 3 separate cores are requested from the same biopsy site for each biopsy procedure. Tumor tissue from FFPE cell pellet material or from bone biopsies is not adequate and should not be provided. Tumor biospecimens should be submitted in the form of a FFPE tumor tissue block. If FFPE tissue blocks cannot be provided, the tissue should be submitted as FFPE tissue sections that are 4-5 microns thick on unstained, unbaked, slides (Superfrost Plus Gold or equivalent) that are freshly cut (ie, cut no more than 30 days prior to shipment to the central laboratory).

- Blood samples will be collected from the start of screening as indicated in the respective sub-study SoAs. The samples will be stored as whole blood, plasma, or serum.

Optional samples for biomarker research that should be collected from participants in the study as appropriate are the following:

- Sections of tumor samples that are collected after initiation of study therapy are requested for assessment of treatment-related changes in tumor phenotype or mechanisms of resistance.

Samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

8.8.1. Specified Gene Expression (RNA) Research

RNA may be isolated from qualifying tumor and blood specimens. The isolated RNA may be subjected to next-generation sequencing in order to define transcriptome profiles associated with effect of study treatment or clinical outcomes.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.8.2. Specified Protein Research

Tumor specimens will be analyzed by immunohistochemistry and/or immunofluorescence. The results may be used to confirm study eligibility as specified for the combination (*biospecimen to confirm eligibility*). Available tissue may be used to characterize quantity and location of cells and proteins that may be associated with effect of study treatment or clinical outcomes.

4-mL blood sample for protein analyses will be collected. The sample(s) will be analyzed for proteins and polypeptides that may be associated with effect of study treatment or clinical outcomes.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

8.8.3. Specified Metabolomic Research

4-mL blood sample for metabolomic analyses may be collected for analysis of metabolites that may be associated with effect of study treatment or clinical outcomes.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

8.9. Immunogenicity Assessments

Immunogenicity blood samples will be assayed for ADA using a validated assay. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Samples tested positive for ADA will be further analyzed for NAb using a validated assay in compliance with Pfizer standard operating procedures. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual. As part of understanding the PK of the study drugs, samples may be used for additional characterization of an observed immunogenicity response and/or evaluation of the bioanalytical methods. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

8.9.1. Immunogenicity Assessment of Sasanlimab

Blood samples (6 mL whole blood at each time point) for evaluation of immunogenicity (ADA) of sasanlimab will be collected from all participants at the time points as outlined in the respective sub-study SoAs.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters evaluated in this study will be specified in the respective sub-study SoAs (Section 12.8.5 for Sub-Study A).

8.11. End of Treatment (EOT) Visit

Participants who discontinue study treatment will undergo the EOT visit and obtain assessments per the respective sub-study SoA. The EOT assessments will be conducted at the visit that the participant is discontinued from study treatment or no longer than 1 week after the decision to discontinue the participant from study drug. The tumor assessments must be completed if not completed in the last 8 weeks and prior response is other than PD. Laboratory assessments must be completed if not completed in the prior 7 days.

If the EOT visit falls within 7 days of the 30-day follow-up visit, the EOT visit can be used to satisfy the requirements for both visits.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

For estimands refer to the respective appendix for each sub-study. For Sub-Study A, refer to Section 12.3; for Sub-Study B, refer to Section 13.3.

9.2. Sample Size Determination

Approximately 375 participants are expected to be assigned to study intervention based on eligibility, assuming that 5 combinations will be initially explored in the umbrella study; refer to the respective sub-study appendix for the sample size determination for each sub-study.

9.2.1. Phase 1b Dose Finding

The total number of participants will depend on the number of dose levels and escalation and de-escalations needed to determine the MTD/RP2D of each combination and the number of participants evaluable for DLT at each dose level.

For details of each sub-study's Phase 1b dose finding refer to the respective appendix.

9.2.2. Phase 2 Dose

After the RP2D of a combination is determined, the study will proceed to Phase 2 to assess efficacy. Details of each sub-study's respective Phase 2 design and sample size is in an appendix.

9.3. Analysis Set

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set	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 a 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. These criteria will be pre-specified in the statistical analysis plan. The per protocol analysis set will be used for sensitivity analyses of the primary efficacy endpoint.
DLT-Evaluable analysis set	The DLT-evaluable analysis set includes all participants who receive at least 1 dose of study treatment in the 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. All participants deemed non-evaluable for DLT may be replaced.
Biomarker analysis set	The biomarker analysis set for each biomarker 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 measurement for the measured analytes related to the study drug (ie, sasanlimab, etc).

Participant Analysis Set	Description
	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 (ie, sasanlimab, etc).

9.4. Statistical Analyses

The SAP will be developed and finalized for each sub-study before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

Each sub-study will be reported separately and by Phase 1b and Phase 2.

9.4.2. Primary Endpoint(s)

Phase 1b

DLT during the DLT-observation period is the primary safety endpoint of the Phase 1b for the combination evaluated. Analyses of DLT are based on the DLT-evaluable analysis set.

Phase 2

Refer to sub-study appendices for primary efficacy endpoints.

9.4.3. Secondary Endpoints

9.4.3.1. Efficacy Analysis

Refer to sub-study appendices for secondary efficacy analyses.

9.4.3.2. Safety Analyses

All safety analyses will be performed on the safety population.

Simple summary statistics (descriptive) will be presented for participants with SAEs, AEs of special interest, laboratory abnormalities, and other secondary safety endpoints during the on-treatment period (defined as the time from the first dose of study treatment through minimum of 30 days after last dose of study treatment or the start day of new anti-cancer drug – 1 day) unless otherwise specified in the SAP.

9.4.3.2.1. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using the MedDRA. AE data will be reported in tables and listings. Summaries of AEs by mapped terms, appropriate thesaurus level, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death and premature

withdrawal from study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized. Listings of DLTs and deaths will be provided.

9.4.3.2.2. Laboratory Test Abnormalities

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay using shift tables. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.4.3.3. PK Analyses of Sasanlimab

Concentrations for sasanlimab will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by arm, cycle, and day.

PK parameters including C_{trough}, C_{max}, T_{max}, and AUC for sasanlimab will be determined from the respective concentration-time data using standard non-compartmental methods as data permit. Additionally, if data permit or if considered appropriate, PK parameters such as $t_{½}$, CL, and V_d will also be estimated. Actual sample collection times will be used for the parameter calculations. Non-compartmental PK parameters, when calculated, will be summarized descriptively by sub-study and cycle.

The trough concentrations for sasanlimab will be plotted for each combination arm using a box whisker plot by cycle and day to assess the attainment of steady state.

Summary data may be compared with the historical data of sasanlimab and combination study drugs as single agents to assess any potential drug interaction effects.

9.4.3.4. Analysis of Immunogenicity Data of Sasanlimab

For the immunogenicity data, the percentage of participants with positive ADA and NAb (if analyzed) each will be summarized by dose level or 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.

9.4.4. Exploratory Endpoints

9.4.4.1. Analyses of Biomarker Endpoints

Summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined for baseline and on-treatment biomarkers. Those biomarkers showing significant association (at significance level of 0.05) with objective response rate will be used to define participant subgroups for time-to-event analyses. Further details will be specified in the SAP.

9.4.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

9.4.5.1. Electrocardiogram Analyses

ECG measurements (either single measurement or an average of the triplicate measurements when available) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, RR interval, PR interval, QRS complex, and QTc.

Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post baseline corrected QT interval.

9.4.6. Other Analyses

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

PK, efficacy, biomarker, and safety data from both Part 1 and Part 2 of a sub-study may be pooled for PK/PD analyses using appropriate modeling to explore any association between study drug exposure, biomarkers, safety, and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately.

Potential impact of immunogenicity on PK, clinical responses, and safety/tolerability may be explored, if data warrant, and may be reported separately.

9.5. Interim Analyses

Interim analyses will be determined by sub-study and details provided in each corresponding Appendix as necessary.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an

internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

Surveillance for SAEs according to regulatory guidelines.

Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level performed in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

As this is an open-label study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose de-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 30 days from the previous ICD signature date.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Exploratory Analyses Results Reporting

Results from exploratory analyses will be reported in the CSR where possible. However, given the exploratory nature of the objectives and endpoints, the analyses may not be completed at the time of the CSR. Results from exploratory analyses that are not included in the CSR will be shared with the scientific community through publication at scientific conferences and/or in peer-reviewed scientific journals.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

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

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

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

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

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

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the clinical monitoring plan.

10.1.8. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study portal and study team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA of each sub-study. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. Local laboratories may be used for all protocol-specified laboratory assessments. Local laboratories to be used must be confirmed acceptable by the investigator and submit reference range documents for each test utilized.

Samples for all laboratory assessments in Table 4 will be drawn at the time points indicated in the respective sub-study Schedule of Activities. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit. Additional laboratory assessments may be required for the sub-studies and will be listed in the respective appendices.

Table 4. Master Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry[a]		
Hemoglobin Platelet count WBC count Absolute neutrophils Absolute Lymphocytes Absolute Monocytes Absolute Eosinophils Absolute Basophils	ALT AST Bicarbonate or CO_2 CRP Alkaline phosphatase Sodium Potassium Magnesium Chloride Total calcium Total bilirubin Total protein BUN or urea Creatinine Creatinine clearance[b] Uric acid Glucose (random) LDH Albumin Phosphorus or Phosphate Amylase Lipase	**Serology** Hepatitis B surface (HBV) Hepatitis C antibody (HCV) **Coagulation** INR aPTT or PTT **Urinalysis** Protein (qual) Blood (qual) Microscopic analysis (Reflex Testing)[c]	**Other** FSH (if applicable) **Endocrinology** ACTH TSH Free T4 **Pregnancy Test** For female participants of childbearing potential, serum or urine.

a. For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.
b. Estimated creatinine clearance according to Cockcroft-Gault formula, or by 24-hour urine collection, or according to local institutional method.
c. Only required if urine dipstick is positive for blood or protein. If ≥2+ protein on urine dipstick, collect spot urine sample to calculate UPCR or collect 24 hr urine.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

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

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE: • Is associated with accompanying symptoms. • Requires additional diagnostic testing or medical/surgical intervention. • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE as per Section 8.3.8.1. Also, “lack of efficacy” or “failure of expected pharmacological action” does not constitute an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

An SAE is defined as any untoward medical occurrence that, at any dose:
Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section). • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study investigation under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

AE and SAE Recording/Reporting

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

Assessment of Causality

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraceptive guidance and collection of pregnancy information is included in the respective sub-study appendices (Section 12.10.2 for Sub-Study A; Section 13.10.2 for Sub-Study B).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.7.1) will be stored for up to 15 years or other period as per local requirements.

    - Samples for banking will be stored indefinitely or for another period as per local requirements (Section 8.7.2).

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

10.8. Appendix 8: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator for study participants, users, and other persons. This definition also includes events related to procedures for study participants only. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

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

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe

An SAE is an AE that:
A permanent impairment of a body structure or a body function. Inpatient or prolonged hospitalization, Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

SADE Definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.8.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP Manual.

AE, SAE and Device Deficiency Recording

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality

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

Assessment of Causality
• The causality assessment is one of the criteria used when determining regulatory reporting requirements
Follow-up of AE/SAE/Device Deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

SADE Reporting to Pfizer Safety
• Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al (2009).[19]

Categorizing Lesions at Baseline

Measurable Lesions

Lesions that can be accurately measured in at least 1 dimension.

Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).

Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.

Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline (Screening visit). Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be inevaluable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed post-baseline.

If 2 target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

Measurements for target lesions that become small should continue to be recorded. If the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate too small to measure and judged to be less than 10 mm and 5 mm will be used as a default measurement in the calculation of the sum of the diameters.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INEVALUABLE, PRESENT WITHOUT UNEQUIVOCAL PROGRESSION, UNEQUIVOCAL PROGRESSION. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Objective response status at each evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case should be discussed with the radiologist and the sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

Target Disease

Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.

Stable Disease : Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable Disease can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.

Progressive Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

Not evaluable (NE): Progression has not been documented, and

- 1 or more target lesions have not been assessed; or
- Assessment methods used were inconsistent with those used at baseline; or
- 1 or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or
- 1 or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target Disease

CR: Disappearance of all non-target lesions and normalization of tumor marker levels (if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) above the normal limits.

PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of stable disease or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

Not evaluable (NE): Progression has not been determined and 1 or more non-target lesion sites have not been assessed or assessment methods used were inconsistent with those used at baseline or 1 or more non-target lesions cannot be assessed (eg, poorly visible or unclear

images) or 1 or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Participants requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document PD even after discontinuation of study treatment.

Determination of Tumor Response by RECIST

When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized in the following table.

Objective Response Status at Each Assessment for Participants with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
Stable Disease	Non-PD* or not all evaluated	No	Stable Disease
Not Evaluable	Non-PD	No	Not Evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

*Non PD includes CR and Non CR/Non PD
** New lesions must be unequivocal

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of Stable Disease, follow up measurements must have met the Stable Disease criteria at least once after start of the treatment at a minimum interval of 6 weeks.

10.10. Appendix 10: Management of Immune-Related Adverse Events (irAEs) for Sasanlimab

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over Baseline Colitis: asymptomatic	-Continue study treatment -Symptomatic treatment (eg loperamide)	-Close monitoring for worsening symptoms. -Educate participant to report worsening immediately. -If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	-Withhold study treatment - Symptomatic treatment	-If improves to Grade ≤1: Resume study treatment. -If persists >5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 hours; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	-Withhold for Grade 3 -Permanently discontinue study treatment for Grade 4 or recurrent Grade 3 -1.0 to 2.0 mg/kg/day prednisone IV or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider lower endoscopy	-If improves: -Continue steroids until Grade ≤1, then taper over at least 1 month; resume study treatment following steroids taper (for initial Grade 3). -If worsens, persists >3 to 5 days, or recurs after improvement. -Add infliximab 5 mg/kg (if no contraindication). -Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	-Continue study treatment -Symptomatic therapy (for example, antihistamines, topical steroids)	-If persists >1 to 2 weeks or recurs: -Withhold study treatment -Consider skin biopsy -Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study treatment following steroids taper. -If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: Life threatening consequences	-Withhold study treatment for Grade 3 -Permanently discontinue for Grade 4 or recurrent Grade 3 -Consider skin biopsy -Dermatology consult -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections	-If improves to Grade ≤1: -Taper steroids over at least 1 month; resume study treatment following steroids taper (for initial Grade 3).

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	-Consider withholding study treatment -Monitor for symptoms every 2 to 3 days -Consider Pulmonary and Infectious Disease consults	-Re-assess at least every 3 weeks. -If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	-Withhold study treatment -Pulmonary and Infectious Disease consults -Monitor symptoms daily; consider hospitalization -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider bronchoscopy, lung biopsy	-Re-assess every 1 to 3 days If improves: -When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume study treatment following steroids taper. -If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	-Permanently discontinue study treatment. -Hospitalize -Pulmonary and Infectious Disease consults -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider bronchoscopy, lung biopsy	-If improves to Grade ≤1: -Taper steroids over at least 1 month. -If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT >ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	-Continue study treatment	-Continue liver function monitoring -If worsens: Treat as Grade 2 or 3 - 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	-Withhold study treatment -Increase frequency of monitoring to every 3 days	-If returns to Grade ≤1: -Resume routine monitoring; resume study treatment. -If elevation persists >5 to 7 days or worsens: -Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	-Permanently discontinue study treatment -Increase frequency of monitoring to every 1 to 2 days -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consult gastroenterologist/ hepatologist -Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	-If returns to Grade ≤1: -Taper steroids over at least 1 month. -If does not improve in >3 to 5 days, worsens or rebounds: -Add mycophenolate mofetil 1 gram (g) twice daily. -If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased >ULN to 1.5 x ULN	-Continue study treatment	-Continue renal function monitoring. -If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN	-Withhold study treatment -Increase frequency of monitoring to every 3 days -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections -Consider renal biopsy	-If returns to Grade ≤1: -Taper steroids over at least 1 month, and resume study treatment following steroids taper. -If worsens: -Treat as Grade 4.
Grade 4 Creatinine increased >6 x ULN	-Permanently discontinue study treatment -Monitor creatinine daily -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections Consider renal biopsy -Nephrology consult	-If returns to Grade ≤1: Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin I, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	-Withhold study treatment - Hospitalize -In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management -Consult cardiologist to establish etiology and rule-out immune-mediated myocarditis -Guideline based supportive treatment as per cardiology consult* -Consider myocardial biopsy if recommended per cardiology consult	-If symptoms improve and immune-mediated etiology is ruled out, re-start study treatment. -If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	-Permanently discontinue study treatment -Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections	-Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A, abatacept).

*Suggested guidelines include: Local guidelines, ESC, or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Continue study treatment -Endocrinology consult if needed -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate -Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	-Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Withhold study treatment -Consider hospitalization - Endocrinology consult -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate -Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	-Resume study treatment once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). -Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/ Hypophysitis (secondary endocrinopathies)	-If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): -Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) -Hormone replacement/suppressive therapy as appropriate -Perform pituitary MRI and visual field examination as indicated **-If hypophysitis is confirmed:** -Continue study treatment if mild symptoms with normal MRI. Repeat the MRI in 1 month	-Resume study treatment once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). -In addition, for hypophysitis with abnormal MRI, resume study treatment only once shrinkage of the pituitary gland on MRI/CT scan is documented. -Continue hormone replacement/suppression therapy as appropriate.

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
	-Withhold study treatment if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month -Add prophylactic antibiotics for opportunistic infections	

Other irAEs* (not described above)		
Grade of other irAEs (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	-Withhold study treatment pending clinical investigation	-If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting study treatment -If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	-Withhold study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Specialty consult as appropriate	-If improves to Grade ≤1: -Taper steroids over at least 1 month and resume study treatment following steroids taper.
Recurrence of same Grade 3 irAEs	-Permanently discontinue study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Specialty consult as appropriate	-If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4	-Permanently discontinue study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed -Add prophylactic antibiotics for opportunistic infections -Specialty consult	-If improves to Grade ≤1: Taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	- Permanently discontinue study treatment -Specialty consult	

* Refer to Section 6.6.1 for irAE management principles based on AE severity.
For sasanlimab as the backbone therapy for combinations with different molecular-targeted agents, potential overlapping toxicities can be expected. For other irAEs not specifically covered in this table (such as uveitis), refer to the NCCN Management of Immunotherapy-Related Toxicities for detailed guidance: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

10.11. Appendix 11: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
1L	first-line
ACTH	adrenocorticotropic hormone
ADA	antidrug antibodies
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AHA	American Heart Association
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
aRCC	advanced renal cell carcinoma
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AV	atrioventricular
BCG	Bacille Calmette Guérin
BCRP	breast cancer resistance protein
BID	twice a day
Bini	binimetinib
BLRM	Bayesian Logistic Regression Model
BNP	brain natriuretic peptide
bp	blood pressure
bpm	beats per minute
BRAF	B-Raf proto-oncogene serine/threonine protein kinase
BUN	blood urea nitrogen
BVN	bivariate normal
cfDNA	cell-free DNA
CDx	companion diagnostic
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CK-MB	creatine kinase-muscle type, myocardial band
CL	total clearance of drug from serum
C_{max}	maximum concentration

Abbreviation	Term
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	Clinical Study Report
CT	computed tomography clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	trough concentrations
C_{trough}-DN	dose-normalized trough concentration
CV	coefficient of variation
CXDX	Cycle X Day X
CYP	Cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DHP	dihydropyridine
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DR	duration of response
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
Enco	encorafenib
EOI	end of infusion
EOT	end of treatment
ERK	extracellular receptor kinase
ESC	European Society of Cardiology
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)

Abbreviation	Term
EWOC	escalation with overdose control
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GH	growth hormone
GI	gastrointestinal
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HFSR	hand-foot skin reaction
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
ID	identification
IFN	interferon
Ig	immunoglobulin
IGF-1	insulin-like growth factor 1
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ISR	injection site reaction
IV	intravenous(ly)
IWR	interactive Web-based response
JM	juxta-membrane
KRAS	Kirsten rat sarcoma

Abbreviation	Term
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAD	maximum administered dose
MAP	meta-analytic-predictive
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MHC	major histocompatibility complex
mOS	median overall survival
mPFS	median progression-free survival
MRI	magnetic resonance imaging
msec	Millisecond(s)
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition
N/A	not applicable
NAb	neutralizing antibodies
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
ND	next dose
NE	not evaluable
NGS	next generation sequencing
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OCT	organic cation transporter
OD	overdose
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease or disease progression pharmacodynamic
PD-1	programmed death - 1
PDGFR	platelet-derived growth factor receptor
PD-L1/PD-L2	programmed death ligand-1 / programmed death ligand-2
PDx	programmed death - 1, - L1, or - L2
PE	physical examination

Abbreviation	Term
PET	positron emission tomography
PFS	progression-free survival
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PRL	prolactin
PRO	Patient Reported Outcomes
Pr(OD)	probability of overdosing
Pr(TT)	probability of target toxicity
pT	probability of toxicity
PT	prothrombin time
PTT	partial thromboplastin time
PTEN	phosphatase and tensin homolog
PVC	premature ventricular contraction/complex
QD	once daily
Q3W	every 3 weeks
Q4W	every 4 weeks
QRS	Q wave, R wave and S wave
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
RPED	retinal pigment epithelial detachment
RVO	retinal vein occlusion
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SC	Subcutaneous(ly)
SD	standard deviation
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
ST-T	ST-segment and T-wave

Abbreviation	Term
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal phase half-life
T4	thyroxine
TBili	total bilirubin
TCR	T-cell receptor
TdP	Torsades de Pointes
TGF	transforming growth factor
TIGIT	T cell immunoreceptor with Ig and ITIM domains
T_{max}	time to reach maximum concentration
TNF	tumor necrosis factor
TNM	Tumor Node Metastasis
TPS	Tumor Proportion Score
TSH	thyroid-stimulating hormone
TT	target toxicity
TTR	time to tumor response
UC	urothelial carcinoma
UD	under dose
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
UPCR	urinary protein creatinine ratio
UPM	unit probability mass
US	United States
USADE	unanticipated serious adverse device effect
V_d	volume of distribution
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WOCBP	woman of childbearing potential

10.12. Appendix 12: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer. Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.12.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per Exclusion criterion #4, Active infections requiring systemic therapy, or Exclusion criterion #13 Participants with active, uncontrolled viral infection. When the infection resolves, the patient may be considered for re-screening.

10.12.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant treatments or changes in concomitant treatments since the last contact.
- Review and record contraceptive method and results of pregnancy testing if applicable for the participant. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 10.12.3.1 of this appendix regarding pregnancy tests.
- Assess ECOG performance status.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.12.3. Alternative Facilities for Safety Assessments

Alternative facilities to the study site may be used as described in this section.

10.12.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. Participants may have safety labs completed at a local laboratory even in the absence of a public emergency; however, this section is included to highlight the option to use local labs if needed to facilitate collection of safety laboratory assessments during a public emergency. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology panel
- Chemistry panel
- Endocrinology
- Coagulation panel
- Pregnancy test (if applicable)

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. Decisions about dose modifications (if applicable) based on results of the local laboratory tests remains the responsibility of the investigator or medically qualified staff. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the eCRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the eCRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.12.3.2. Electrocardiograms, MUGA/Echocardiograms, Visual Acuity Exams (when required per the SOA)

If the participant is unable to visit the study site for ECGs, MUGA/Echo, or the eye exams, the participant may visit an alternative facility to have these assessments performed. Qualified study site personnel must order, receive, and review results. Participants may have these procedures completed at an alternative facility to the site even in the absence of a public emergency; however, this section is included to highlight the option to use an alternative facility if needed to allow completion of procedures during a public emergency.

10.12.4. Study Intervention

Investigational product that can be orally administered at home may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of the study interventions must be kept in the participant's source documents/medical records.

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

The guidance below is intended to support decision making, but it is not meant to supersede clinical assessment of any individual study participant case.

Regarding the continued administration of study drug treatment to ongoing participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection, the following is recommend:

- For symptomatic participants with active SARS-CoV2 infection, study drug treatment should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. It is requested that the site inform the study team when study drug treatment is restarted.
- Continue to consider potential drug-drug interactions for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.12.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities if feasible and locally permitted. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. All assessments must be performed by someone meeting local requirements for performing the assessments. The following may be performed during a home health visit (when required per the SOA):

- Physical Examination
- Weight
- Vital Signs
- ECG

- Dermatologic Exam
- Visual Acuity Exam
- ECOG performance status
- Laboratory sample collection of tests listed in Section 10.12.3.1 of this appendix.
- PROs
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant treatments or changes in concomitant treatments since the last contact.
- Review and record contraceptive method if applicable for the participant. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.12.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study sponsor.

10.12.7. Efficacy Assessments

If the participant is unable to visit the study site for CT/MRI, the participant may visit an alternative facility to have the CT/MRI performed. Qualified study site personnel must order, receive, and review results. Participants may have imaging completed at an alternative facility to the site even in the absence of a public emergency; however, this section is included to highlight the option to use an alternative facility if needed to allow completion of imaging during a public emergency.

10.13. Appendix 13: Potential Drug-Drug Interactions

This section presents examples of drugs that are referenced in the sub-studies as either prohibited or to be taken with caution; it does not contain a complete list of potential drug-drug interactions. Please refer to the Concomitant Therapy section of the master protocol (Section 6.5) and the respective sub-study appendices (Sub-Study A: Section 12.6.5) for comprehensive concomitant therapy requirements and restrictions for sasanlimab and the combination therapies.

Examples of Strong and Moderate CYP3A4 Inhibitors

Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors
elvitegravir/ritonavir (RIT) indinavir or indinavir/RIT lopinavir/RIT nelfinavir ritonavir saquinavir or saquinavir/RIT tipranavir/RIT danoprevir/RIT telaprevir itraconazole ketoconazole clarithromycin mibefradil conivaptan mifepristone voriconazole nefazodone cobicistat boceprevir posaconazole telithromycin troleandomycin grapefruit juice paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) posaconazole ritonavir telaprevir telithromycin troleandomycin Pomegranates, star fruits, Seville oranges, and juice of any of these products	aprepitant ciprofloxacin conivaptan cyclosporine diltiazem dronedarone erythromycin fluconazole fluvoxamine tofisopam verapamil

Examples of CYP3A4 inhibitors from fda.gov and University of Washington Drug Interaction Database, not considered exhaustive. Potent CYP3A4 inhibitors are defined as those drugs that increase the AUC of oral midazolam or other CYP3A4 substrates ≥5-fold. Moderate inhibitors are defined as those drugs that increase the AUC of oral midazolam or other CYP3A4 substrates CYP3A4 ≥2 to <5-fold.

Examples of Strong and Moderate CYP3A Inducers

Strong CYP3A Inducers	Moderate CYP3A Inducers
St. John's Wort avasimibe carbamazepine mitotane phenobarbital phenytoin rifampin rifapentine apalutamide enzalutamide ivosidenib lumacaftor	bosantan efavirenz etavirine primidone

Examples of CYP3A inducers from fda.gov and University of Washington Drug Interaction Database, not considered exhaustive.
Strong CYP3A inducers are defined as those drugs that decrease the AUC of CYP3A substrates ≥80%.
Moderate CYP3A inducers are drugs that decrease the AUC of CYP3A substrates by ≥50% to 80%.

Examples of P-gp Inhibitors

P-gp Inhibitors
elvitegravir/ritonavir (RIT) indinavir or indinavir/RIT lopinavir/RIT nelfinavir ritonavir saquinavir or saquinavir/RIT tipranavir/RIT danoprevir/RIT telaprevir itraconazole ketoconazole clarithromycin mibefradil conivaptan mifepristone

As the list of medications with potential drug-drug interactions is a dynamic list continually changing when new information becomes available, the following websites should be used when a concomitant medication is considered to be either prohibited or to be taken with caution as referenced in the sub-study appendices (eg, a moderate or strong CYP3A, P-gp, or UGT1A1 inhibitor and/or inducer):

- FDA list of examples of clinical substrates, inhibitors, and inducers of CYP and/or UGT enzymes:
    - https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1
    - https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2
    - https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3
- FDA list of examples of clinical substrates and inhibitors of transporters:
    - https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1
    - https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2
- University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/)
- Literature including lists of potential UGT1A1 perpetrators:
    - Xia Lv, Yangliu Xia, Moshe Finel, Jingjing Wu, Guangbo Ge, Ling Yang. Recent progress and challenges in screening and characterization of UGT1A1 inhibitors. Acta Pharmaceutica Sinica B. 2019; 9(2): 258-278. https://doi.org/10.1016/j.apsb.2018.09.005

10.14. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	N/A
Protocol Amendment 1	04 August 2020	• A visit was added for Cycle 5, Day 8 to collect a sasanlimab PK sample and perform an ECG assessment at the sasanlimab T_{max} at steady-state. • Blood sample collection for sasanlimab PK and immunogenicity assessments was extended to occur every 6 months after Cycle 13 until End of Treatment. • Modified DLT criterion #8 to differentiate thresholds between Grade 3 and 4 non-hematologic laboratory abnormalities, and modified DLT criterion #9 to add liver function laboratory abnormality thresholds in addition to Hy's Law. • Modified Inclusion criterion #6 to clarify that patients with locally advanced disease must not be amenable for definitive therapy. • For Sub-Study A, added clarification of known and potential overlapping toxicities between sasanlimab and encorafenib plus binimetinib in Section 12.2.3.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	N/A
Protocol Amendment 2	07 December 2020	• Details from Sub-Study A were removed from the Synopsis (Section 1.1) to focus the Protocol Summary on the high-level aspects of this umbrella study and direct readers to the sub-study appendices for additional details. • The Clinical Overview of sasanlimab was updated to reflect data from the recently revised IB and publication (Section 2.2.2). • The sasanlimab fixed dose was updated in the master protocol to reflect that either 300 mg Q4W or CCI will be administered in the sub-studies, and a justification for the CCI dose was provided (Sections 4.1, 4.3.1, 6.1). The starting dose for Sub-Study A was moved from the master protocol to Sub-Study A section (Section 12.4.4.1). • DLT criterion #4 was modified to not overlap with criterion #5 (Section 4.3.3). • Master Inclusion criterion #10 was deleted from the master protocol (Section 5.1) because the requirements for tumor specimens will vary depending on the patient population and molecular testing specific to each sub-study, and therefore will be included in each sub-study appendix.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	N/A
		• Master Inclusion criterion #11 was edited to clarify the minimum life expectancy for previously treated participants (Section 5.1). • Master Exclusion criterion #8 was edited to remove the requirement that patients with asymptomatic brain metastasis need to be off anti-epileptic therapy, as per Investigator feedback and consistency with study ARRAY-818-202 (Section 5.1). • Instructions for Allocation to Study Intervention, including IRT wording, was moved from Sub-Study A (Section 12.6.1.1) to the master protocol (Section 6.3.1) because it will apply to all sub-studies. • It was clarified in the master protocol that therapeutic use of steroids may be allowed according to the toxicity management guidelines in each sub-study; instructions were also added to clarify that sasanlimab should not be resumed during such use of steroids, as indicated in the IB (Section 6.5.6). • The timeframe for long-term follow-up visits/survival visits was updated from 90 days or 3 months to 12 weeks for consistency with the sasanlimab program (Sections 8.1.3, 12.1). • It was clarified in Section 8.3.7 that progression of the malignancy under study is not to be captured as

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	N/A
		an SAE unless it results in fatal outcome, to align with Section 10.3.2. • Instructions for tumor tissue samples were updated to allow for fine needle aspiration to ease site and subject burden, and to remove the number of required slides because this may differ for each sub-study and phase (Sections 8.8 and 12.8.4). • Number of participants in the master protocol was edited to remove specifics and instead refer to the respective sub-studies, due to variations in numbers and design among sub-studies (Sections 1.1, 9.2). • CO_2 is now allowed in lieu of bicarbonate clinical laboratory testing (Section 10.2). • Instructions for measurable lesions by X-ray were removed because X-ray is not allowed for tumor assessments in this study (Section 10.9). • Guidance for Alternative Measures During Public Emergencies was added per Pfizer new standard (Section 10.12). • List of CYP3A inhibitors and inducers was moved from Sub-Study A Section 12.10.3 to master protocol Section 10.13, as it will apply to multiple sub-studies. Drugs were also added to these lists.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	N/A
		• List of P-gp inhibitors was added to master protocol Section 10.13. • Sentence that was applicable only to Sub-Study A was moved from the CYP3A appendix (12.10.3) to Sub-Study A Section 12.6.5.1.1. • In Sub-Study A SoA, the rows for Echocardiogram/MUGA and dermatologic exam were re-formatted to clarify that Echocardiogram/MUGA is required at EOT visit and the dermatologic exam is required at EOT and Day 30 visit (Section 12.1). • Patient Reported Outcomes of EORTC QLQ-C30/LC13 were added as required procedures and secondary outcomes in Sub-Study A on Day 1 of each Cycle in Phase 2 (Sections 12.1, 12.3, 12.8.5, 12.9.1.5.2.6). • Post-baseline ECOG assessments were removed from Sub-Study A as they will not be used for data analysis (Section 12.1). • Blood volumes for PK and immunogenicity sampling were added to Sub-Study A SoA footnotes and predose restrictions were modified because they do not affect the PK analysis (Section 12.1). • Sub-Study A SoA footnote for tumor history (footnote g) was clarified to include molecular profiling data, if available, in

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	N/A
		accordance with Master protocol Section 8.8 (Section 12.1). • Sub-Study A SoA footnotes for biospecimen eligibility confirmation (footnote dd) and tumor biopsies (footnote ee) were modified to reflect that tumor tissue is only required for Phase 2 because it may not be feasible to provide sufficient archived tumor specimens or perform new biopsies for NSCLC patients after multiple lines of therapy (Section 12.1). • PD-L1 expression in baseline tumor samples was removed as a secondary objective/endpoint from Sub-Study A Phase 1b because it may not be feasible to provide sufficient archived tumor specimens or perform new biopsies for NSCLC patients after multiple lines of therapy (Section 12.3). • Examples of PK parameters were removed from the PK Endpoint in Sub-Study A to allow flexibility in PK analysis, and the description of PK analyses was updated (Section 12.3, 12.9.1.5.2.3). • Wording for the PD-L1 expression objective and endpoint in Phase 2 of Sub-Study A was adjusted for clarity (Section 12.3). • Sub-study Inclusion criterion #16 regarding tumor specimens in Sub-Study A was edited to apply only to Phase 2 and to clarify what constitutes sufficient tumor sample, in accordance with the removal of

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	N/A
		the PD-L1 expression secondary endpoint in Phase 1b (Section 12.5.1). • Radiologic images will not need to be sent to a central vendor for Phase 1b subjects in Sub-Study A because efficacy is not a primary endpoint or focus for Phase 1b of Sub-Study A (Section 12.8.1.1). • Specifications for tumor samples in Sub-Study A were modified to reflect the modified Sub-Study A SoA and modified Sub-Study A Inclusion criteria (Section 12.8.4). • Administrative changes were made to improve readability and consistency of structure and wording across the sub-studies and master protocol.
Protocol Amendment 3	28 April 2021	• Exclusion criterion for QTcF was moved from the Master Protocol (Section 5.2) and will be added to the Sub-Study-specific exclusion criteria as appropriate because QT prolongation/cardiac events are not currently a risk specific to sasanlimab, but may be risks for the combination drugs. • Information was added regarding the administration of sasanlimab [redacted] dose from vials (Section 6.1.1). • Edited language for study discontinuation per the updated sponsor protocol template (Section 7.2). • Added a 180-day post-last-dose follow-up visit, and added home

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	18 June 2020	N/A
		pregnancy tests for the follow-up visits, in accordance with the Clinical Trial Facilitation Group (CTFG) *Recommendations related to contraception and pregnancy testing in clinical trials* (Sections 8.2.5, 8.2.8, 12.1). • Timeframe of 5-10 minutes was added to the triplicate ECGs in the ECG assessment instructions (Section 8.2.3) and the SoA footnotes (Section 12.1). • Added Sub-Study B (sasanlimab + axitinib + SEA-TGT) to Section 13. • Figure 2 was updated to better reflect Sub-Study A design. • Administrative changes were made to improve readability and consistency of structure and wording across the sub-studies and master protocol.

11. REFERENCES

1. Johnson ML, Braiteh F, Grilley-Olson JE, et al. Assessment of Subcutaneous vs Intravenous Administration of Anti-PD-1 Antibody PF-06801591 in Patients With Advanced Solid Tumors: A Phase 1 Dose-Escalation Trial. JAMA Oncol. 2019;5(7):999-1007.

2. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(22):2078-92.

3. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819-30.

4. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.

5. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.

6. NCCN. National Comprehensive Cancer Network. NCCN Guidelines Version 3.3030. Non-small cell cancer: NCCN evidence blocks. 2020. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx#nscl. Accessed on: 31 Mar 2020.

7. TAXOTERE (docetaxel). US Prescription Information (USPI); May 2010 2018, Bridgewater, NJ: Sanofi-Aventis U.S. LLC. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210498lbl.pdf.

8. Cretella D, Digiacomo G, Giovannetti E, et al. PTEN Alterations as a Potential Mechanism for Tumor Cell Escape from PD-1/PD-L1 Inhibition. Cancers (Basel). 2019;11(9).

9. Mariathasan S, Turley SJ, Nickles D, et al. TGFbeta attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature. 2018;554(7693):544-48.

10. Perea F, Sanchez-Palencia A, Gomez-Morales M, et al. HLA class I loss and PD-L1 expression in lung cancer: impact on T-cell infiltration and immune escape. Oncotarget. 2018;9(3):4120-33.

11. Ascierto PA, Ferrucci PF, Fisher R, et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. Nat Med. 2019;25(6):941-46.

12. Taylor MH, Lee C-H, Makker V, et al. Phase IB/II Trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. J Clin Oncol. 2020;38:1154-63.

13. McCoach CE, Blumenthal GM, Zhang L, et al. Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small-cell lung cancer treated with a targeted therapy or immunotherapy. Ann Oncol. 2017;28(11):2707-14.

14. Pfizer. PF-06801591 Investigator's Brochure Document on file. 2020.

15. Choi BC, Penkov K, Bondarenko I, et al., editors. Updated results of subcutaneous anti-programmed cell death 1 receptor antibody sasanlimab (PF-06801591) for locally advanced or metastatic non-small cell lung cancer or urothelial carcinoma. European Society for Medical Oncology; September 18-20, 2020.

16. Edge SB, Byrd DR, Carducci MA, et al. AJCC cancer staging manual. 6497th ed. Springer New York; 2010.

17. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24(19):3187-205.

18. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

20. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18(10):1307-16.

21. Ascierto PA, Dummer R. Immunological effects of BRAF+ MEK inhibition. Oncoimmunology. 2018;7(9):e1468955.

22. Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or

encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19(10):1315-27.

23. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603-15.

24. BRAFTOVI (encorafenib). US Prescription Information (USPI); June 2018 2018, Boulder, CO: Array BioPharma Inc. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210496lbl.pdf.

25. MEKTOVI (binimetinib). US Prescription Information (USPI); June 2018 2018, Boulder, CO: Array BioPharma Inc. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210498lbl.pdf.

26. Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17(9):1248-60.

27. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367(18):1694-703.

28. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867-76.

29. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877-88.

30. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30-9.

31. Urner-Bloch U, Urner M, Jaberg-Bentele N, et al. MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: Long-term ophthalmic effects. Eur J Cancer. 2016;65:130-8.

32. Array BioPharma. Binimetinib Investigator's Brochure. Document on file. 2019.

33. Array BioPharma. Encorafenib Investigator's Brochure. Document on file. 2019.

34. Kefford R, Arkenau H, Brown M, et al. Phase I/II study of GSK2118436, a selective inhibitor of oncogenic mutant BRAF kinase, in patients with metastatic melanoma and other solid tumors. Journal of Clinical Oncology. 2010;28(15_suppl):8503-03.

35. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

36. Bergman B, Aaronson NK, Ahmedzai S, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-42.

37. Neuenschwander B, Matano A, Tang Z, et al. A Bayesian industry approach to phase I combination trials in oncology. In *Statistical Methods in Drug Combination Studies*. Chapman & Hall/CRC Biostatistics Series. Edited by: Zhao W, Yang H. 2015. p. 95-135.

38. Neuenschwander B, Capkun-Niggli G, Branson M, et al. Summarizing historical information on controls in clinical trials. Clin Trials. 2010;7(1):5-18.

39. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian approaches to clinical trials and health-care evaluation. 13. John Wiley & Sons; 2004.

40. Fayers P, Aaronson N, Bjordal K, et al. EORTC QLQ-C30 Scoring Manual (ed 3). Brussels, Belgium. EORTC publications; 2001.

41. Pfizer. Axitinib Investigator's Brochure Document on file. 2020.

42. Schiller JH, Larson L, Ignatius Ou SH, et al. Efficacy and safety of axitinib in patients with advanced non–small-cell lung cancer: results from a phase II study. J Clin Oncol. 2009;27(23):3836-41.

43. INLYTA (axitinib). US Prescription Information (USPI); June 2020 2020: Pfizer, Inc. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=759.

44. Gálffy G, Lugowska I, Poddubskaya E, et al., editors. JAVELIN Medley VEGF: a phase 2 study of avelumab + axitinib in patients with previously treated nonsmall cell lung cancer (NSCLC) or treatment-naive, cisplatin-ineligible urothelial cancer (UC). Society for Immunotherapy of Cancer (SITC) 35th Anniversary Annual Meeting; 2020.

45. Seattle Genetics. SGN-TGT Investigator's Brochure Document on file. 2019.

46. Bendell JC, Bedard P, Bang Y.-J., et al., editors. Phase Ia/Ib dose-escalation study of the anti-TIGIT antibody tiragolumab as a single agent and in combination with atezolizumab in patients with advanced solid tumors. AACR; 2020.

47. Rodriguez-Abreu D, Johnson ML, Hussein MA, et al. Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). J Clin Oncol. 2020;38:9503.

48. Ahn M, Niu J, Kim D, et al. Vibostolimab, an anti-TIGIT antibody, as monotherapy and in combination with pembrolizumab in anti-PD-1/PD-L1-refractory NSCLC. Ann Oncol. 2020;31:S754-S840.

49. Niu J, Nagria A, Voskoboynik M, et al. Safety and efficacy of vibostolimab, an anti-TIGIT antibody, plus pembrolizumab in patients with anti-PD-1/PD-L1-naive NSCLC. Ann Oncol. 2020;31:S754-S840.

50. Patil N, Cho BC, Johnson ML, et al., editors. Efficacy of tiragolumab + atezolizumab in PD L1 IHC and TIGIT subgroups in the phase II CITYSCAPE study in first-line NSCLC. World Conference on Lung Cancer; 2020; Singapore.

51. Kudo M. Scientific rationale for combined immunotherapy with PD-1/PD-L1 antibodies and VEGF inhibitors in advanced hepatocellular carcinoma. Cancers.12(5):1089.

52. Powles TB, Loriot Y, Bellmunt J, et al. Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma (UC): association between clinical outcomes and exploratory biomarkers. Ann Oncol. 2020;31:S552-3.

53. Neal JW, Lim FL, Felip E, et al. Cabozantinib in combination with atezolizumab in NSCLC patients previously treated with an immune checkpoint inhibitor: results from cohort 7 of the COSMIC-021 study. J Clin Oncol. 2020;38:9610.

54. Ji Y, Wang S-J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol. 2013;31(14):1785-91.

12. APPENDIX A: SUB-STUDY A: SASANLIMAB + ENCORAFENIB + BINIMETINIB

12.1. Schedule of Activities (SoA): Sub-Study A

The SoA table provides an overview of the sub-study visits and procedures. Refer to Section 8 of the master protocol and Section 12.8 of this sub-study appendix for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule unplanned visits in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant, or if otherwise clinically indicated.

Table 5. Schedule of Activities Sub-Study A Phase 1b and Phase 2

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11, Section 10.11	Screening[b] (≤28 days prior to first dose)	Treatment Period										Follow-Up[e]		
		Cycle 1[c] (Days 1 to 28)			Cycle 2[c] (Days 1 to 28)		Cycle 3 & 4 (Days 1 to 28)	Cycle 5 (Days 1 to 28)		Cycle ≥6 (Days 1 to 28)				
		Day 1	Day 8 (Phase 1b Only)	Day 15	Day 1	Day 15	Day 1	Day 1	Day 8 (Phase 1b Only)	Day 1	EOT[d]	Day 30[e]	Day 60, Day 90, Day 180 [e]	Survival[e]
Visit Window			±1	±2	±2	±2	±2	±2	±1	±2		±7	±7	±7
Informed consent[f]	X													
Tumor and medical history[g]	X													
Substance and tobacco use	X										X			
Physical examination[h]	X	X	X	X	X		X	X		X	X			
Height	X													
Weight	X	X			X		X	X		X	X			
Vital signs (BP/pulse rate/ temp)[i]	X	X	X	X	X		X	X		X	X	X		
ECOG performance status[j]	X	X												
Triplicate 12-lead ECG[k]	X	X												
Single 12-lead ECG[k]			X	X	X		X	X	X	X	X	X		
Echocardiogram/MUGA[l]	X						X (C3 only)			C6D1, C9D1, C12D1, and every 6 months thereafter	X			
Ophthalmic examination[m]	X													
Visual acuity exam[m]	X	X			X		X	X		X				
Dermatologic exam	X	X					X (C3 only)	X		C7D1 and then every	X	X		

Table 5. Schedule of Activities Sub-Study A Phase 1b and Phase 2

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11, Section 10.11	**Screening**[b] **(≤28 days prior to first dose)**	**Treatment Period**										**Follow-Up**[e]		
		Cycle 1[c] **(Days 1 to 28)**			**Cycle 2**[c] **(Days 1 to 28)**		**Cycle 3 & 4 (Days 1 to 28)**	**Cycle 5 (Days 1 to 28)**		**Cycle ≥6 (Days 1 to 28)**				
		Day 1	**Day 8 (Phase 1b Only)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 8 (Phase 1b Only)**	**Day 1**	**EOT**[d]	**Day 30**[e]	**Day 60, Day 90, Day 180** [e]	**Survival**[e]
										8 weeks thereafter				
Laboratory Assessments of Hematology and Blood Chemistry[n]	X	X	X	X	X	X	X	X		X	X	X		
Coagulation[n]	X	X			X		X	X		X	X	X		
Urinalysis[o]	X	X									X	X		
Pregnancy test[p]	X	X			X		X	X		X	X	X	X	
Hepatitis B, C tests[q]	X													
Endocrinology tests[n]	X						Every 4 cycles starting at C4D1							
Allocation to study intervention[r]		X												
Administration of study treatment (sasanlimab)[s]		X			X		X	X		X				
Administration of study treatment (encorafenib)[t]		Continuous QD												
Administration of Study treatment (binimetinib)[u]		Continuous BID												
Dispensing of encorafenib and binimetinib		X			X		X	X		X				
Local site injection tolerability assessment[v]		X			X		X	X		X				
Tumor assessment[w]	X	Every 8 wks (±7 days) from C1D1 for the first 18 months, then every 12 wks (±7 days) thereafter according to calendar, regardless of treatment delays and until progressive disease assessed by investigator using RECIST v1.1 or start of new anti-cancer therapy												
Patient Reported Outcomes: EORTC QLQ-C30/LC13[x]		X			X		X	X		X	X			

Table 5. Schedule of Activities Sub-Study A Phase 1b and Phase 2

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11, Section 10.11	Screening[b] (≤28 days prior to first dose)	Treatment Period										Follow-Up[e]		
		Cycle 1[c] (Days 1 to 28)			Cycle 2[c] (Days 1 to 28)		Cycle 3 & 4 (Days 1 to 28)	Cycle 5 (Days 1 to 28)		Cycle ≥6 (Days 1 to 28)				
		Day 1	Day 8 (Phase 1b Only)	Day 15	Day 1	Day 15	Day 1	Day 1	Day 8 (Phase 1b Only)	Day 1	EOT[d]	Day 30[e]	Day 60, Day 90, Day 180 [e]	Survival[e]
Nonserious and serious adverse events[y]	X	→	→	→	→	→	→	→	→	→	→	→	→	→
Prior and Concomitant medication/surgery/ radiation & non-drug supportive interventions[z]	X	X	X	X	X	X	X	X	X	X	X	X		
Survival & subsequent anti-cancer therapy											X	X	X	X
Contraception check[aa]	X	X			X		X	X		X	X	X	X	
Remote visit						X							X	X
PK, Pharmacodynamic, Pharmacogenomic, and Immunogenicity														
Sasanlimab PK[bb]		X	X	X	X		X (C3 only)	X	X	X (C7, C10, C13, then every 6 cycles until EOT)				
Encorafenib PK[cc]		X		X	X			X						
Binimetinib PK[cc]		X		X	X			X						
Blood biospecimen to confirm eligibility[dd]	X													
Baseline tumor biopsy[ee]	X													
Biobanked biospecimen for genetics[ff]		X												

Table 5. Schedule of Activities Sub-Study A Phase 1b and Phase 2

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11, Section 10.11	Screening[b] (≤28 days prior to first dose)	Treatment Period										Follow-Up[e]		
		Cycle 1[c] (Days 1 to 28)			Cycle 2[c] (Days 1 to 28)		Cycle 3 & 4 (Days 1 to 28)	Cycle 5 (Days 1 to 28)		Cycle ≥6 (Days 1 to 28)				
		Day 1	Day 8 (Phase 1b Only)	Day 15	Day 1	Day 15	Day 1	Day 1	Day 8 (Phase 1b Only)	Day 1	EOT[d]	Day 30[e]	Day 60, Day 90, Day 180 [e]	Survival[e]
Blood for cell-free (cf) DNA analysis[gg]		X			X		X (C3 only)				X			
Blood for specified genetic research[hh]	X	X		X	X		X (C3 only)							
Blood for T-Cell Receptor (TCR) analysis[kk]	X	X		X	X		X (C3 only)							
Immunogenicity for sasanlimab[ll]		X			X		X (C3 only)	X		X (C7, C10, C13, and then every 6 cycles until EOT)	X			

a. Day relative to start of study intervention (Day 1).
b. **Screening:** To be performed within 28 days prior to first dose. Visit may be conducted over multiple days.
c. For Phase 1b, during Cycle 1, the D1, D8, and D15 visits occur in clinic. For Phase 1b, during Cycle 2, only D1 visit occurs in clinic and for D15 only clinical laboratory assessments will be performed. For Phase 2, during Cycle 1, Day 1 visit occurs in clinic, no Day 8 visit occurs, and Day 15 will be on-site full visit. For Phase 2 Cycle 2, Day 1 in clinic and Day 15 labs occur locally.
d. **End of Treatment (EOT) Visit:** See Section 8.11. Conducted at the visit that the participant is discontinued from study treatment or no longer than 1 week after the decision to discontinue the participant from study drug.
e. **Follow-up:** See Section 8.2.8. The initial safety follow-up visit will be conducted at the study clinic 30 days after the last dose of study drug. The 60, 90, and 180-day follow-up may be conducted by remote contact (eg. telephone). **Survival Follow-up:** See Section 8.1.3. Only to be performed for participants enrolled in Phase 2. Participants will be contacted every 12 weeks (±7 days) after the last clinic visit until death, lost-to-follow-up, study discontinued by sponsor, end of study, or participant withdrawal of consent of study, whichever comes first.
f. **Informed Consent:** Must be obtained prior to undergoing any study specific procedures. May be obtained more than 28 days prior to first dose.

Table 5. Schedule of Activities Sub-Study A Phase 1b and Phase 2

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11, Section 10.11	Screening[b] (≤28 days prior to first dose)	Treatment Period										Follow-Up[e]		
		Cycle 1[c] (Days 1 to 28)			Cycle 2[c] (Days 1 to 28)		Cycle 3 & 4 (Days 1 to 28)	Cycle 5 (Days 1 to 28)		Cycle ≥6 (Days 1 to 28)				
		Day 1	Day 8 (Phase 1b Only)	Day 15	Day 1	Day 15	Day 1	Day 1	Day 8 (Phase 1b Only)	Day 1	EOT[d]	Day 30[e]	Day 60, Day 90, Day 180 [e]	Survival[e]

g. **Tumor History:** Includes history of disease under study including details of primary diagnosis, treatment history, staging, and molecular profiling data (if available). **Medical History:** Includes history other than the cancer under study. Abnormalities observed during screening are to be considered as medical history.
h. **Physical examination (PE):** See Section 8.2.1.
i. **Vital Signs:** See Section 8.2.2. Includes temperature, blood pressure (BP), pulse rate. On Day 1 of each cycle, vital signs are to be measured prior to administration of any study drug (pre-dose).
j. **Eastern Cooperative Oncology Group (ECOG) Performance Status:** See Section 8.2.6.
k. **Triplicate/Single 12 Lead electrocardiogram (ECG):** See Section 8.2.3. When triplicate ECG is requested, 3 serial 12-lead ECGs will be conducted within approximately 5-10 minutes total time. Triplicate ECGs on C1D1 will be collected prior to administration of any study drug. For remaining timepoints, single ECG will be collected prior to administration of study drug. When coinciding with blood sample draws for PK, ECG assessment is to be performed prior to blood sample collection, such that the blood sample is collected at the nominal time.
l. **Echocardiogram or multigated acquisition (MUGA) Scan:** Section 12.8.2.1. The same modality used during screening is to be used for all subsequent timepoints. Assessment will also be performed if a participant experiences an AE which may be related to cardiac dysfunction in the opinion of the investigator.
m. **Ophthalmic Examination:** See Section 12.8.2.3.
n. **Hematology, Blood Chemistry, Endocrinology, and Coagulation assays:** See Appendix 2 (Section 10.2) and Section 12.10.1 for Laboratory Tests list. Not necessary to repeat on C1D1 if performed within 7 days prior to C1D1 as part of Screening. Subsequent assessments must be performed within 72 hours prior to the scheduled visit. Hematology and chemistry assessments on Cycle 2 Day 15 may be drawn at a lab local to the participant and do not require on-site visit.
o. **Urinalysis:** Dipstick is acceptable. No need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. See Section 10.2 and Section 12.10.1 for urinalysis details.
p. **Pregnancy Test (Serum/Urine):** For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy, once at screening and once at the C1D1 visit before dosing. Participants with a confirmed positive pregnancy test(s) must not be dosed. Pregnancy tests will also be routinely performed throughout the study as per SoA and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be performed if requested by IRB/EC or if required by local regulations. At the 60, 90, and 180-day remote follow-up visits, pregnancy tests may be conducted via home kits.

Table 5. Schedule of Activities Sub-Study A Phase 1b and Phase 2

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11, Section 10.11	Screening[b] (≤28 days prior to first dose)	Treatment Period										Follow-Up[e]		
		Cycle 1[c] (Days 1 to 28)			Cycle 2[c] (Days 1 to 28)		Cycle 3 & 4 (Days 1 to 28)	Cycle 5 (Days 1 to 28)		Cycle ≥6 (Days 1 to 28)				
		Day 1	Day 8 (Phase 1b Only)	Day 15	Day 1	Day 15	Day 1	Day 1	Day 8 (Phase 1b Only)	Day 1	EOT[d]	Day 30[e]	Day 60, Day 90, Day 180 [e]	Survival[e]

q. **Hepatitis B, C:** In the case of apparent ongoing HBV or HCV infection, reflex serum viral load testing will be performed.
r. **Allocation:** The participant allocation number will be assigned using an IRT system. Participants can be allocated in IRT no more than 3 days prior to dosing.
s. **Study Treatment (sasanlimab):** Will be administered once every 28 days as 1 SC injection totaling 300 mg.
t. **Study Treatment (encorafenib):** Once daily oral administration. See Section 12.6 for details.
u. **Study Treatment (binimetinib):** Twice daily oral administration. See Section 12.6 for details.
v. **Local Site Injection Tolerability Assessment for sasanlimab:** See Section 8.2.7.
w. **Tumor Assessments:** See Section 8.1.1 and Section 12.8.1.1. Tumor response assessments will be determined in accordance with RECIST v1.1.
x. **Patient Reported Outcome:** Required in Phase 2 only. The questionnaires should be administered prior to any other scheduled assessments or drug administrations. See Section 12.8.5.
y. **Nonserious and Serious AE Assessments:** See Section 8.3. AEs and SAEs are documented and recorded at each visit using NCI CTCAE version 5.0.
z. **Concomitant Medications and Non-Drug Supportive Interventions:** Includes supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions). Reporting period for concomitant medications for AEs and SAEs are to follow respective AE and SAE reporting period.
aa. **Contraceptive Check:** See Section 12.10.2. Male participants who are able to father children and female participants who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected methods of contraception throughout the study and continue for 6 months after the last dose. The investigator or his or her designee will discuss with the participant the need to use the appropriate contraception methods consistently and correctly and document such conversation in the participant's chart. The investigator or his or her designee will instruct the participant to call immediately if the selected contraception methods are discontinued, or if pregnancy is known or suspected in the participant or participant's partner.
bb. **Blood for sasanlimab PK:** One 3-mL sample will be drawn for sasanlimab on each day indicated on the SOA. All samples taken on Day 1 of a cycle will be collected within 6 hours prior to dosing of sasanlimab.
cc. **Blood for encorafenib and binimetinib PK:** One 5-mL sample will be drawn for both encorafenib and binimetinib PK on each day indicated on the SOA. All samples will be collected within 2 hours prior to dosing of either encorafenib or binimetinib.
dd. **Biospecimen to confirm eligibility:** See Section 8.7.1. A 20-mL blood sample will be collected to confirm eligibility via ctDNA assay. In Phase 2, if ctDNA assay results cannot be interpreted, reflex testing of tumor tissue will be initiated. This blood sample may also be used for possible future development of a medical device/diagnostic test (See Section 12.8.4).

Table 5. Schedule of Activities Sub-Study A Phase 1b and Phase 2

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11, Section 10.11	Screening[b] (≤28 days prior to first dose)	Treatment Period										Follow-Up[e]		
		Cycle 1[c] (Days 1 to 28)			Cycle 2[c] (Days 1 to 28)		Cycle 3 & 4 (Days 1 to 28)	Cycle 5 (Days 1 to 28)		Cycle ≥6 (Days 1 to 28)				
		Day 1	Day 8 (Phase 1b Only)	Day 15	Day 1	Day 15	Day 1	Day 1	Day 8 (Phase 1b Only)	Day 1	EOT[d]	Day 30[e]	Day 60, Day 90, Day 180 [e]	Survival[e]

ee. **Baseline Tumor Biopsy:** For Phase 2 only, participants will submit a tumor biospecimen obtained by a procedure performed prior to Cycle 1 Day 1. The tumor specimen may be used for specified analyses (Sections 8.7.1 and 8.8.2) or exploratory biomarker analysis (Section 8.8).

ff. **Banked biospecimen for genetics:** A 4-mL blood sample will be collected on Cycle 1 Day 1 prior to dosing with any study drug and retained in a biobank for possible assessments of genes and other analytes (eg, proteins, RNA, nondrug metabolites), unless prohibited by local regulations or by decision of the institutional review board or ethics committee (Section 8.7.2).

gg. **Blood for cell-free (cf) DNA Analysis:** A 20-mL blood sample for preparation of plasma will be collected prior to dosing with any study drug, and on Day 1 of Cycles 2 and 3 for exploratory analyses as described in Section 8.7.1.

hh. **Blood for specified genetic research:** A 4-mL whole blood sample will be collected prior to dosing with any study drug for exploratory genetic and epigenetic analyses as described in Section 8.7.1.

ii. NA.

jj. NA.

kk. **Blood for T-Cell Receptor (TCR) Analysis:** A 6-mL whole blood sample will be collected into a tube optimized for DNA preservation prior to dosing with any study drug on specified visits (Section 8.7.1).

ll. **Blood for sasanlimab Immunogenicity (anti-drug antibody [ADA] and neutralizing antibodies [NAb]) Testing:** One 6-mL sample will be drawn on each day indicated in the SoA. All samples taken on Day 1 of a cycle will be taken within 6 hours prior to sasanlimab dosing.

12.2. Introduction for Sub-Study A

12.2.1. Study Rationale

There are several common treatment options for advanced/metastatic $BRAF^{V600}$ NSCLC (per current NCCN guidelines). These include treatment with single-agent pembrolizumab (anti-PD-1) for PD-$L1^{high}$ tumors and anti-PD-1/chemotherapy. However, the highest response rate reported for these tumors is with the combination of dabrafenib, targeting $BRAF^{V600}$ and a MEK inhibitor, trametinib, where the reported response rate was 64%.[20] Dabrafenib/trametinib has become a standard of care for the treatment of $BRAF^{V600}$ advanced/metastatic NSCLC. However, tumor responses observed with dabrafenib/trametinib are not durable, as the percentage of treated patients who maintained responses for 10.4 months is only 32%.[20] There is evidence that BRAF + MEK inhibitor combinations can stimulate anti-tumor immunity.[21] However, in doing so, there is likely to be induction of immune checkpoints, such as PD-L1, that can limit anti-tumor activity.[20] Clinical studies in patients of $BRAF^{V600}$-mutant melanoma treated with triplet therapies containing a PD-1 or PD-L1 inhibitor plus a BRAF + MEK inhibitor doublet provide evidence that combining the PD-1/PD-L1 inhibitors with targeted therapy yields an improvement in the durability of responses and trends toward improvement in PFS and OS. ORR was comparable between the targeted agents alone and the triplets.[11,12] Therefore, in Sub-Study A, a triplet combination of sasanlimab, encorafenib, and binimetinib will be evaluated to assess safety and clinical activity in patients with advanced/metastatic $BRAF^{V600}$-mutant NSCLC.

12.2.2. Background

Encorafenib is a potent and selective ATP-competitive inhibitor of $BRAF^{V600}$-mutant kinase. Mutations in the BRAF gene, such as $BRAF^{V600E}$, can result in constitutively activated BRAF kinase that may stimulate tumor cell growth. Encorafenib inhibited in vitro growth of tumor cell lines expressing $BRAF^{V600\ E,\ D,\ and\ K}$ mutations.

Binimetinib is a potent and selective allosteric, ATP-uncompetitive inhibitor of MEK1/2. MEK proteins are upstream regulators of the ERK pathway. In vitro, binimetinib inhibited ERK phosphorylation in cell-free assays as well as viability and MEK-dependent phosphorylation of BRAF-mutant human melanoma cell lines. Binimetinib also inhibited in vivo ERK phosphorylation and tumor growth in BRAF-mutant murine xenograft models.[22,23]

Encorafenib and binimetinib target 2 different kinases in the RAS/RAF/MEK/ERK pathway. Compared with either drug alone, co-administration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in BRAF mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in $BRAF^{V600E}$-mutant human melanoma xenograft studies in mice. Additionally, the combination of encorafenib and binimetinib delayed the emergence of resistance in $BRAF^{V600E}$-mutant human melanoma xenografts in mice compared to either drug alone.[21]

Encorafenib 450 mg orally QD in combination with binimetinib 45 mg orally BID have received marketing approval for the treatment of patients with unresectable or metastatic melanoma with a $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation in several jurisdictions, including the

US and EU (BRAFTOVI® [encorafenib] prescribing information; MEKTOVI® [binimetinib] prescribing information). Regulatory approval of encorafenib and binimetinib in combination was based on the Phase 3 COLUMBUS study (Study CMEK162B2301 [NCT01909453]; randomized, 2-part, open-label, multicenter, international clinical study).[24,25]

See the master protocol Introduction (Section 2) for background on sasanlimab.

12.2.2.1. Clinical Overview: Clinical Safety of Encorafenib in Combination with Binimetinib

COLUMBUS results demonstrated improved tolerability in the encorafenib 450 mg QD + binimetinib 45 mg BID arm compared with single-agent encorafenib 300 mg QD.[22,23] This is consistent with a body of literature that suggests the combination of a BRAF inhibitor and a MEK inhibitor results in improved tolerability compared with either agent alone.[26-30]

Among participants receiving encorafenib plus binimetinib combination therapy in the COLUMBUS study, the most frequent adverse events (≥20% of participants, all grades) were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), arthralgia (26%), myopathy (23%), hyperkeratosis (23%), rash (22%), headache (22%), constipation (22%), visual impairment (20%) and serous retinopathy (20%). Most of these toxicities were generally reversible and manageable by supportive medical care, dose modifications or discontinuation. Other clinically important adverse events occurring in <10% of participants were facial paresis, pancreatitis, panniculitis, drug hypersensitivity and colitis. The most frequent laboratory abnormalities (≥2%, Grade 3 or 4) were increased GGT (11%), increased ALT (6%), increased creatine phosphokinase (5%), increased fasting glucose (5%), increased creatinine (4%), anemia (4%), hyponatremia (4%), increased AST (3%), neutropenia (3%) and lymphopenia (2%).

Important potential adverse events associated with the administration of the combination of encorafenib and binimetinib established primarily from safety data from the COLUMBUS study and, where indicated, from other studies of the combination, include:

New primary malignancies: Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Cutaneous and non-cutaneous malignancies occurred in participants, including cutaneous squamous carcinoma/keratoacanthoma (2.6%; median time to first occurrence of 5.8 months) and basal cell carcinoma (1.6%).

Left ventricular dysfunction: Symptomatic or asymptomatic decreases in ejection fraction occurred in 7% of patients, with Grade 3 left ventricular dysfunction occurring in 1.6% of participants.

Hemorrhage: Hemorrhage occurred in 19% of participants, with events ≥Grade 3 occurring in 3.2% of participants. Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of participants. The most frequent hemorrhagic events

were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%).

Venous thromboembolism: Occurred in 6% of participants, including 3.1% of participants who developed pulmonary embolism.

Ocular toxicities: Serous retinopathy is a class effect of MEK inhibitors. It is generally asymptomatic or mildly symptomatic and reversible.[31] Serous retinopathy occurred in 20% of participants. Symptomatic serous retinopathy occurred in 8% of participants with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. RVO is a known class-related adverse reaction of MEK inhibitors and may occur in participants treated with binimetinib in combination with encorafenib. In participants with BRAF mutation-positive melanoma across multiple clinical trials, 0.1% of participants experienced RVO.

Pneumonitis/Interstitial Lung Disease: Pneumonitis occurred in 0.3% of participants with BRAF mutation-positive melanoma across multiple clinical trials.

Hepatotoxicity: The incidence of Grade 3 or 4 increases in liver function laboratory tests was 6% for ALT, 2.6% for AST and 0.5% for alkaline phosphatase. No participant experienced Grade 3 or 4 serum bilirubin elevation.

CK Elevation/Rhabdomyolysis: Asymptomatic elevations of laboratory values of serum CK occurred in 58% of participants. Rhabdomyolysis was reported in 0.1% of participants with BRAF mutation-positive melanoma across multiple clinical trials.

QTc Prolongation: QT prolongation has been observed in participants treated with BRAF inhibitors. Encorafenib is associated with dose-dependent QTc interval prolongation in some participants. In the COLUMBUS study, an increase in QTcF to >500 msec was measured in 0.5% of participants.

Embryo-Fetal Toxicity: Encorafenib or binimetinib can cause fetal harm when administered to pregnant women.

Detailed information regarding clinical safety is presented in the respective IBs for encorafenib and binimetinib.[32,33]

12.2.3. Benefit/Risk Assessment

The primary risks of the combination of encorafenib plus binimetinib treatment are included in the respective product labels and include known class effects of BRAF and MEK inhibitors in the treatment of patients with melanoma. The combination of encorafenib plus binimetinib has a lower frequency and severity of pyrexia compared with dabrafenib plus trametinib. For the encorafenib/binimetinib doublet, almost all cases of pyrexia presenting as an SAE were associated with secondary causes of infection of progressive melanoma. The safety of encorafenib/binimetinib in the first- or second-line treatment of advanced/metastatic $BRAF^{V600}$ NSCLC is under active clinical investigation in a separate study (NCT03915951).

While no detailed safety analyses are available for this study, the doses listed in the respective product labels of 450 mg encorafenib QD and 45 mg binimetinib BID have been tolerated. Detailed information regarding nonclinical studies and clinical PK are presented in the respective IBs for encorafenib and binimetinib, which are the SRSDs for this study.

For the triplet combination of sasanlimab with encorafenib/binimetinib there is a low likelihood of combinatorial toxicities based on the frequency of events observed in the clinic for these agents. In Study B8011001 of single-agent sasanlimab, there was 1 case of pneumonitis out of 106 participants evaluated in the SC expansion cohorts. In the COLUMBUS study of encorafenib in combination with binimetinib, the incidence of pneumonitis was 0.3%. It is expected that pneumonitis will be remain uncommon in the triplet combination and measures are included in this protocol to guide dosing and use of concomitant therapy for treatment emergent pneumonitis. The other class of AE where there is the potential for combinatorial toxicity is hepatotoxicity. Liver function test abnormalities (ALT elevations) of at least Grade 3 were observed in 6% of participants treated with encorafenib/binimetinib in the COLUMBUS study and 1 out of 106 participants treated with sasanlimab. Lower level elevations were also observed in these studies and there is the potential for additive effects. Adding the observed frequencies of AEs for these 3 agents, the frequency of Grade 3 or higher AEs with the potential for overlapping toxicity is expected to be less than 10%. In addition, based on the clinical experience as detailed in the SRSDs for encorafenib and binimetinib and the potential class effect of PD-1 inhibitors overall, other rarely overlapping toxicities may include (but are not limited to) ocular toxicities, skin-related toxicities, nausea/vomiting, diarrhea, cardiac toxicities, and pyrexia. For this reason, the recommended dose modification guidelines for the potential overlapping toxicities are provided in Sections 12.10.4 and 12.10.5.

There is specific guidance to the investigator for dosing and concomitant therapy for participants experiencing both of these classes of AEs, which are considered to be immune-related, in Section 12.6.6.2. Therefore, the guidance in this protocol is expected to mitigate the risk these 2 classes of toxicities which might be increased in frequency and/or severity in this study. Given the expected clinical activity of all 3 agents in previously untreated participants with advanced/metastatic $BRAF^{V600}$-mutant NSCLC the benefit/risk assessment is positive for the initiation of clinical investigation of sasanlimab in combination with encorafenib and binimetinib.

12.3. Objectives, Endpoints, and Estimands for Sub-Study A

The following objectives and endpoints are specific to the Sub-Study A combination of sasanlimab + encorafenib + binimetinib in participants with NSCLC with $BRAF^{V600}$ mutations (Table 6):

Table 6. Sub-Study A Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**

Table 6. Sub-Study A Objectives and Endpoints

Objectives	Endpoints
Phase 1b	**Phase 1b**
• To assess the DLT rate and estimate the MTD of sasanlimab in combination with encorafenib and binimetinib to determine the RP2D for the combination.	• DLTs during the DLT-observation period.
Phase 2	**Phase 2**
• To assess the durable ORR of sasanlimab in combination with encorafenib and binimetinib.	• Durable OR, defined as confirmed CR or 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.	• 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, encorafenib, binimetinib and applicable metabolites (ie, 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 (ie, incidence) against sasanlimab, as data permit.
Phase 2	**Phase 2**
• To assess other measures of anti-tumor activity of sasanlimab in combination with encorafenib and binimetinib.	• OR, DR, TTR, PFS by investigator assessment using RECIST v1.1, and 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 (ie, C_{trough}) when administered in combination, as data permit.

Table 6. Sub-Study A Objectives and Endpoints

Objectives	Endpoints
• To evaluate the immunogenicity of sasanlimab when given in combination with encorafenib and binimetinib.	• ADA and NAb (ie, incidence) against sasanlimab, as data permit.
• To assess the association 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
Exploratory:	**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.	• 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.

Estimands

This section defines the estimands associated with the primary endpoints of the sub-study.

The primary endpoint definitions and the observations that will be considered in the derivation of the endpoints are described or referenced below.

Phase 1:

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 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).

12.4. Study Design for Sub-Study A

See Section 4.1 for the overall study design in the master protocol.

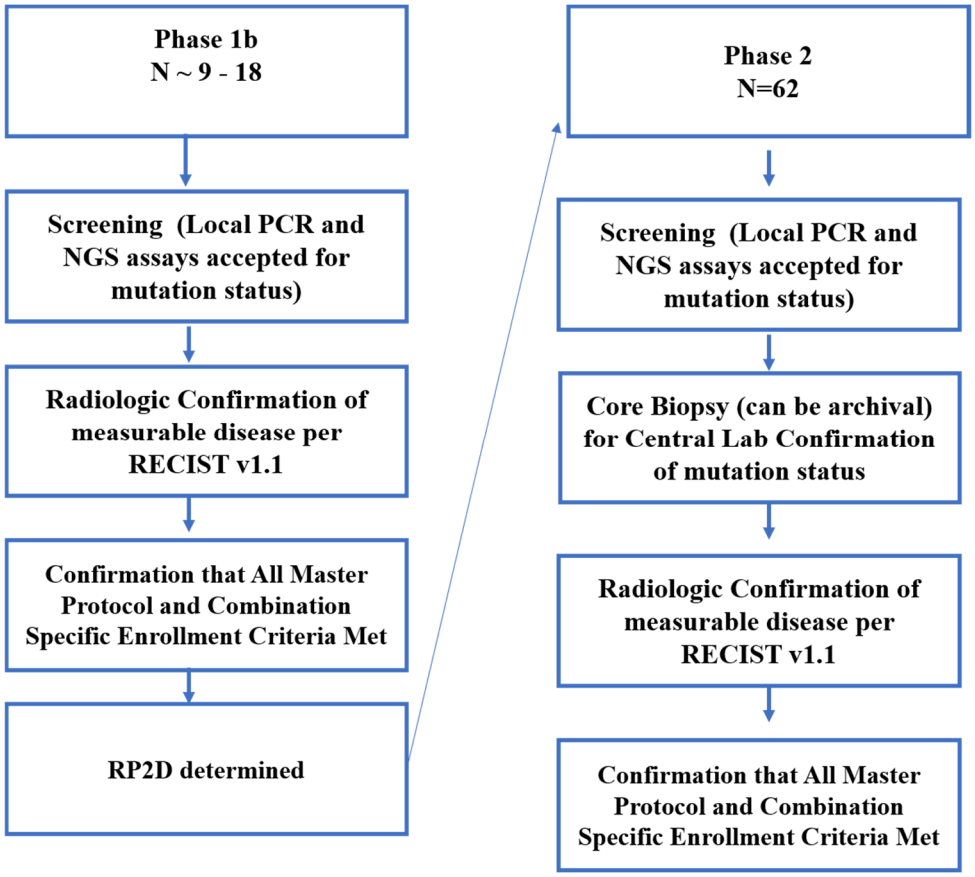
Sub-Study A will start with a Phase 1b safety part with 3 available dose levels (see Table 7). The enrollment criteria for Phase 1b includes participants with $BRAF^{V600}$-mutated NSCLC in any line of therapy. Approximately 9-18 participants will be enrolled in Phase 1b, starting with dose level 0 (Table 7 and Figure 2).

Guidance for Phase 1b dosing (dose level to be evaluated in the next cohort) and enrollment (number of participants to be enrolled in the next cohort) decisions will be based on a

Bayesian Logistic Regression Model (BLRM). The BLRM incorporates single-agent and available combination DLT data (historical and prospectively across dose cohorts) to estimate the posterior probability of under-dosing, target dosing and overdosing, thereby reducing participant risk and increasing efficiency and precision during dose finding with combination treatments.

Phase 2 will begin once the combination RP2D from the Phase 1b is selected. Approximately 62 participants will be enrolled into the Phase 2 part to assess durable OR and participant safety.

Figure 2. Sub-Study A Design



12.4.1. Phase 1b Design

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 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 Section 12.10.6 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.

Table 7. 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.

12.4.2. Phase 2 Design

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

12.4.3. Rationale for the Sub-Study A Combination

See Section 2.1 for the overall study rationale in the master protocol.

Combinations of a BRAF inhibitor with a MEK inhibitor have become a standard in the treatment of participants with $BRAF^{V600}$-mutant melanoma and NSCLC. Clinical and preclinical data suggests that the combination of a BRAF inhibitor such as encorafenib with a MEK inhibitor, such as binimetinib, will promote an anti-tumor immune response in $BRAF^{V600}$-mutant tumors. Clinical and preclinical evidence also suggest that combining

encorafenib and binimetinib with a PD-1 blocking monoclonal antibody, will lead to deeper and more sustained anti-tumor control. Therefore, in this sub-study, a triplet combination of sasanlimab, encorafenib, and binimetinib will be evaluated to assess safety and clinical activity in participants with advanced/metastatic NSCLC.

12.4.4. Justification for Dose in Sub-Study A

12.4.4.1. Starting Dose for Phase 1b

The starting dose of sasanlimab in Sub-Study A is 300 mg Q4W and will remain constant throughout the study. Refer to master protocol Section 4.3 for the justification for this starting dose.

The starting dose level for encorafenib is 300 mg QD and binimetinib is 45 mg BID in combination with sasanlimab. This corresponds to 1 dose level below the labeled doublet dose of 450 mg QD encorafenib and 45 mg BID binimetinib for metastatic melanoma. A subanalysis of the COLUMBUS trial indicated that this dose level was associated with improved tolerability over the 450 mg QD encorafenib and 45 mg BID binimetinib dose level along with comparable clinical activity.[24,25]

12.4.4.2. Criteria for Dose Escalation/De-Escalation

Refer to Section 12.10.6 for criteria for dose escalation/de-escalation via BLRM for Sub-Study A.

12.4.5. Dose Limiting Toxicity

Refer to master protocol Section 4.3.3 for the definition of DLT.

The DLT observation period is the first 28 days starting with the first dose of any study drug in the combination.

12.4.6. Maximum Tolerated Dose

A dose level combination is a potential candidate for being the MTD level when all the following criteria are met:

- ≥6 participants have been treated at that dose;
- Probability of target dosing >50%; and
- Probability of overdosing <25%.

12.4.7. Recommended Phase 2 Dose (RP2D) Definition

Refer to master protocol Section 4.3.5.

12.5. Study Population for Sub-Study A

Participants must meet all of the general inclusion and exclusion criteria as specified in the master protocol (Section 5) plus the following Sub-study A specific inclusion and exclusion criteria.

12.5.1. Inclusion Criteria for Sub-Study A

Phase 1b and Phase 2:

14. $BRAF^{V600E}$ mutation in tumor tissue or plasma as determined by a local laboratory assay and documented in a local pathology report. Other Class 1 $BRAF^{V600}$ mutations (eg, V600K, V600D, and V600R) will be permitted by prior discussion with the sponsor. Only PCR or NGS-based local assay results will be acceptable.

15. Able to swallow, retain, and absorb oral medications.

Phase 1b only:

16. Any line of therapy for locally advanced/metastatic NSCLC. For Stage IIIB, disease relapse during treatment or within 6 months of chemoradiation with durvalumab consolidation will be considered metastatic disease.

Phase 2 only:

17. Previously untreated for locally advanced/metastatic NSCLC.

18. Able to provide a sufficient amount of plasma and tumor (primary or metastatic, archival or newly obtained); approximately 15 slides (minimum of 10 slides) or block are required.

12.5.2. Exclusion Criteria for Sub-Study A

Phase 1b only:

17. Receipt of anticancer medications or investigational drugs within the following intervals before the first dose of study intervention:

    a. ≤14 days for chemotherapy, targeted small-molecule therapy, radiation therapy, or antineoplastic biologic therapy.

    b. ≤14 days or 5 half-lives (minimum of 14 days) for investigational agents or devices. For monoclonal antibodies, <28 days from the last dose.

Phase 2 only:

18. Prior therapy with anti-PD-1, anti-PD-L1, or anti-PD-L2 agents.

Phase 1b and Phase 2:

19. Participants who have documentation of any of the following: activating EGFR mutation (mutations located in exons 18-21), ALK fusion oncogene, or ROS1 rearrangement. Testing for EGFR mutation is required if status is unknown.

20. Prior treatment with any BRAF inhibitor (eg, dabrafenib, vemurafenib, XL281/BMS908662, etc) or MEK inhibitor (eg, trametinib, cobimetinib, selumetinib, RDEA119, etc).

21. History or current evidence of RVO or current risk factors for RVO (eg, uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).

22. Concurrent or anticipated use of a non-topical medication known to be a strong/moderate CYP3A4 inhibitor or CYP3A inducer within 7 days prior to first dose of study intervention and throughout study duration.

23. LVEF <50% as determined by MUGA or echocardiogram.

24. Triplicate average baseline QTcF >450 msec for male participants or QTcF >470 msec for female participants or QTcF >480 msec in participants with right bundle branch block or a history of prolonged QT syndrome.

12.6. Study Intervention for Sub-Study A

Study Treatments:

For purposes of this sub-study, study intervention refers to sasanlimab, encorafenib, and binimetinib. The prefilled syringe of sasanlimab is a medical device. Refer to Section 6.1.1 for details about the administration of sasanlimab.

Participants will receive the following study treatments in each 28-day cycle:

Phase 1b Dose Levels:

Sasanlimab SC, 300 mg (150 mg/mL, 2 mL) prefilled syringe on Day 1 of each cycle

Encorafenib: 300 mg (4 × 75 mg oral capsules) QD (Dose levels 0 and -1), Encorafenib 450 mg (6 × 75 mg oral capsules) QD (Dose level 1).

Binimetinib: 30 mg (2 × 15 mg oral tablets) BID (Dose level -1), 45 mg (3 × 15 mg oral tablets) BID (Dose levels 0 and 1).

Phase 2 Dose Levels:

RP2D/MTD of sasanlimab 300 mg + encorafenib + binimetinib

Table 8. Study Interventions: Sub Study A (Sasanlimab + Encorafenib + Binimetinib)

Intervention Name	Sasanlimab	Encorafenib	Binimetinib
Type	Biologic Product	small molecule product	small molecule product
Dose Formulation	Solution for injection	Capsule	Tablet
Unit Dose Strength	150 mg/mL, 2 mL (300 mg total) pre-filled syringe	75 mg	15 mg
Dosage Level(s)	300 mg Q4W	300 mg QD, 450 mg QD	45 mg BID, 30 mg BID
Route of Administration	Subcutaneous	Oral	Oral
Use	Experimental	Experimental	Experimental
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a 2-mL Prefilled syringe for 300 mg dose. Each prefilled syringe will be labeled as required per country requirement.	Study intervention will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.
Former Names or Aliases	PF-06801591 RN888	BRAFTOVI® LGX818 ONO-7702 W0090	MEKTOVI® ARRAY-438162 MEK162 ONO-7703 W0074

12.6.1. Administration of Encorafenib and Binimetinib

Encorafenib will be self-administered orally without regard to food. Encorafenib should be taken daily in the morning at approximately the same time (± 2 hours) every day. Participants should be directed to take encorafenib and binimetinib together as applicable. If a participant vomits at any time after dosing, the dose should not be re-administered. Doses of encorafenib that are omitted for AEs or any other reason should not be made up during the day, or at the end of the dosing period. Additional information regarding encorafenib administration is provided in the IP Manual.

Binimetinib will be self-administered orally without regard to food. Binimetinib should be taken 12 ± 2 hours apart in the morning and in the evening at approximately the same times every day. Participants should be directed to take binimetinib and encorafenib together as applicable. If a participant vomits at any time after dosing, the dose should not be re-administered, and the participant should take the next scheduled dose. Doses of binimetinib that are omitted for AEs or any other reason should not be made up during the day, or at the

end of the dosing period. Additional information regarding binimetinib administration is provided in the IP Manual.

Encorafenib and binimetinib will begin on Cycle 1 Day 1 and will be self-administered continuously, except on study visit days, when encorafenib and binimetinib will be administered at the study site.

12.6.2. Preparation, Handling, Storage, Accountability, and Dispensing

The participant/caregiver should be instructed to maintain the encorafenib and binimetinib products in the bottles provided throughout the course of dosing and return the bottles to the site at the next study visit. For further details, refer to master protocol Section 6.2.

12.6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label sub-study that will not be randomized.

12.6.3.1. Allocation to Study Intervention

Refer to master protocol Section 6.3.1.

12.6.4. Study Intervention Compliance

Refer to master protocol Section 6.4.

12.6.5. Concomitant Therapy for Sub-Study A

In addition to concomitant therapy instructions and restrictions in the master protocol Section 6.5, the following concomitant therapy instructions and restrictions apply to Sub-Study A.

12.6.5.1. Permitted Concomitant Therapy Requiring Caution and/or Action

12.6.5.1.1. CYP and UGT Substrates and Inhibitors

Encorafenib is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and UGT1A1. It is also a time-dependent inhibitor of CYP3A4, and induced CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C9, CYP3A4 and UGT1A1 or those substrates that have a narrow therapeutic index.

There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for females of childbearing potential during participation in this study.

Caution should be used in participants receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

Encorafenib has been identified to be metabolized by CYP3A4 and to a lesser extent by CYP2C19 in vitro. **Concomitant use of moderate and/or strong CYP3A4 inhibitors should be avoided throughout the study.** If concomitant use of a strong or moderate CYP3A4 inhibitor is unavoidable, consultation with the sponsor is needed prior to concurrent use of moderate or strong CYP3A4 inhibitors as the dose of encorafenib will be adjusted accordingly during coadministration with moderate or strong CYP3A inhibitor concomitant medications. Selection of an alternate concomitant medication with no or minimal enzyme inhibition and/or induction potential is recommended in Sub-Study A when co-administered with encorafenib. Participants must avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study drugs, due to potential CYP3A4 interaction with encorafenib.

In vitro, binimetinib has been identified to be primarily metabolized by glucuronidation (via UGT1A1, with UGT1A3, UGT1A9 and UGT2B7 also contributing). In clinical study sub-analysis, however, there was no apparent relationship observed between binimetinib exposure and UGT1A1 mutation status. In addition, simulations to investigate the effect of atazanavir 400 mg (UGT1A1 inhibitor) on the exposure of binimetinib 45 mg predicted similar binimetinib C_{max} in the presence or absence of atazanavir.[32] The possible extent of drug interactions mediated by UGT1A1 is expected to be minimal, and likely not clinically relevant; however, as this has not been evaluated in a formal clinical study, UGT1A1 inducers or inhibitors should be administered with caution.

For examples of drugs of CYP3A inhibitors to be used with caution or avoided or where to find additional evolving information regarding UGT1A1 perpetrators, please see Section 10.13.

12.6.5.1.2. Transporter Substrates and Inhibitors

In vitro data showed that encorafenib is a substrate of the transporter P-gp. Thus, drugs that are known to inhibit or induce P-gp should be used with caution. Encorafenib is also an inhibitor of P-gp , BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3, and the co-administration of drugs that are substrates of these transporters should be used with caution.

Binimetinib has also been shown to be a substrate of P-gp and BCRP. It is advised that inhibitors and inducers of P-gp and BCRP transporters should be taken with caution when coadministered with binimetinib.

For examples of drugs of P-gp inhibitors to be used with caution, please see Section 10.13.

12.6.5.1.3. Drugs with a Conditional or Possible Risk to Prolong QT Interval and/or Induce Torsade de Pointes

Investigators should use caution when administering encorafenib with concomitant medications with a known, conditional or possible risk to prolong the QT interval and/or induce torsade de pointes. Participants receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication and may

require dose titration of the concomitant medication. See the CredibleMeds® website: Combined List of Drugs That Prolong QT and/or cause Torsades de Pointes (TdP).

12.6.5.2. CYP3A Inducers

Concomitant moderate and/or strong systemic CYP3A inducers, which could significantly decrease the exposure of encorafenib, are prohibited throughout the study (Phase 1 and Phase 2). For examples of moderate and/or strong CYP3A4 inducers, see Section 10.13.

12.6.6. Dose Interruptions and Modifications for Sub-Study A

12.6.6.1. Dose Interruptions

Following initiation of therapy, treatment with encorafenib and binimetinib may be delayed to allow resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the Investigator, would make the participant unsuitable for further participation in the study.

Individual decisions regarding dose interruptions and modifications should be made using appropriate clinical judgment, considering relatedness of the AE to the study treatment and the participant's underlying condition. AEs that have a clear alternative explanation, or transient (≤72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules. The treating physician should refer to and follow the labeled guidance and/or institutional guidelines for the management of toxicities relating to encorafenib and binimetinib.

Some potential immune-related AEs described with anti-PD-1 mAbs, such as sasanlimab, may overlap with encorafenib or binimetinib toxicities (eg, ophthalmologic, cardiovascular, hepatic, pulmonary AEs, etc). The treating physician should make assessment and determine the related component in the combination regimen to manage the AE and make dose interruptions, if needed, accordingly. Consultation with an appropriate specialist is recommended as indicated. Any AE suspected to be immune-related should be managed according to the management guidance of immune-related adverse events in Sections 6.6 and 10.10.

Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment (e.g., elective surgery, unrelated medical events, vacation, holidays). Participants should be placed back on study treatment within 2 weeks (14 days) of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption will be documented in the participant's study record.

If a participant misses >6 weeks (ie, 42 consecutive days) of dosing with encorafenib, study treatment with encorafenib will be permanently discontinued. Due to the potential for limited efficacy of binimetinib alone in the study population, if a participant permanently discontinues treatment with encorafenib, he or she must also permanently discontinue treatment with binimetinib.

If a participant misses >6 weeks (ie, 42 consecutive days) of dosing with binimetinib, study treatment with binimetinib will be permanently discontinued. If a participant discontinues treatment with binimetinib, the participant may continue treatment with encorafenib. Due to the potential for increased toxicity when binimetinib is discontinued, the dose of single-agent encorafenib may need to be decreased in consultation with the sponsor.

12.6.6.2. Dose Modifications

Doses of encorafenib and binimetinib may be independently reduced for toxicity management as outlined in Table 9 and Table 10, respectively. All dose modifications are based on the worst preceding toxicity. The treating investigator should refer to and follow the labeled guidance and/or institutional guidelines for the management of toxicities relating to encorafenib and binimetinib. Detailed guidelines can also be found in Sections 12.10.4 and 12.10.5.

When the AE that resulted in a dose reduction improves to and remains stable to the participant's baseline for a minimum of 14 days, the dose can be re-escalated to the next higher dose level at the discretion of the investigator, provided there are no other concomitant toxicities that would prevent drug re-escalation. There is no limit to the number of times the participant can have their dose reduced or re-escalated; however:

No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTcF ≥501 msec.

No dose re-escalation of binimetinib is allowed after a dose reduction due to LVEF dysfunction.

No dose re-escalation of binimetinib or encorafenib is allowed after a dose reduction due to ocular toxicity ≥Grade 2.

Table 9. Dose Reductions for Encorafenib for Toxicity Management

Encorafenib Starting Dose	Encorafenib First Dose Reduction	Encorafenib Second Dose Reduction
450 mg QD	300 mg QD	225 mg QD
300 mg QD	225 mg QD	150 mg QD

Dose reduction below 75 mg QD of encorafenib is not allowed. Management of participants requiring more than 2 dose reductions of encorafenib (1 dose level decrease at a time) should be discussed with the sponsor.
NOTE: Dose reduction should be based on the highest AE grade.

Table 10. Dose Reductions for Binimetinib for Toxicity Management

Binimetinib Starting Dose	Binimetinib First Dose Reduction	Binimetinib Second Dose Reduction
45 mg BID	30 mg BID	15 mg BID[a]
30 mg BID	15 mg BID[a]	N/A

a. Dose reduction below 15 mg BID of binimetinib is not allowed.
NOTE: Dose reduction should be based on the highest AE grade.

The dose of encorafenib will also be adjusted for participants with concomitant CYP3A4 inhibitors as specified in Section 12.6.5.1.1.

12.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7 of the master protocol for discontinuation of study intervention and participant discontinuation/withdrawal.

12.8. Study Assessments and Procedures for Sub-Study A

See Section 8 for master protocol study assessments and procedures, in addition to the following procedures specific to Sub-Study A.

12.8.1. Efficacy Assessments

12.8.1.1. Tumor Response Assessments

Radiologic images of Phase 2 participants must be made available to a central vendor for potential central imaging reading of tumor assessments.

Refer to Section 8.1.1 for tumor response assessments.

12.8.2. Safety Assessments

12.8.2.1. Echocardiogram/ Multigated Acquisition Scan (MUGA)

LVEF should be assessed by transthoracic echocardiogram or MUGA and performed as outlined in the SoA.

The same modality used during screening should be used for all subsequent timepoints. Additional assessment should also be performed if a participant experiences an AE which may be related to cardiac dysfunction in the opinion of the investigator.

The details of the echocardiogram/MUGA will not be recorded on a CRF; however, any abnormalities detected on the echocardiogram/MUGA will be reported on the medical history or AE CRF as appropriate.

12.8.2.2. Dermatologic Examination

Dermatologic evaluations will be performed at the site by the investigator to monitor for the possible development of keratoacanthoma and/or squamous cell carcinoma, as these have been reported to occur with selective BRAF inhibitor treatment.[27,30,34] This assessment may be performed predose or postdose at the time points specified in the SoA.

In case of occurrence of keratoacanthoma or squamous cell carcinoma, participants will undergo complete surgical excision of the skin lesion following institutional standards. Dermatologic evaluations will be performed by a dermatologist as clinically indicated.

The details of the dermatologic assessment will not be recorded on a CRF; however, any abnormalities detected during the examination will be reported on the medical history or adverse event CRF as appropriate.

12.8.2.3. Ophthalmic and Visual Acuity Examinations

Full ophthalmic examination will be performed by an ophthalmologist and will include best corrected visual acuity, slit lamp examination, intraocular pressure, dilated fundoscopy, and optical coherence tomography. Examination of the retina is required (especially to identify findings associated with RPED, serous detachment of the retina and RVO). Visual acuity tests may be performed by qualified site staff.

Ophthalmic examinations and visual acuity testing will be performed at visits according to the SoA. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow-up as clinically indicated.

The details of the ophthalmic and visual acuity examinations will not be recorded in the CRF; however, any abnormalities detected are to be reported on the AE or medical history CRF as appropriate.

Additional Ophthalmic Testing

Patients with clinical suspicion of retinal abnormalities of any grade (eg, RPED, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity) must complete at least 1 of the following additional assessments:

- For non-vascular abnormalities: optical coherence tomography (spectral domain optical coherence tomography recommended)
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.

Images/results of the ophthalmic examinations (at a minimum, optical coherence tomography and/or fluorescein angiography) must be sent to the investigational site and be maintained in the patient's source document file. These images/results must be made available upon sponsor request.

12.8.3. Treatment of Overdose

There is no antidote known to over-dosage for either encorafenib or binimetinib. Supportive measures should be instituted. Please refer to the respective IBs for more information.

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

12.8.4. Genetics

Results of the local laboratory $BRAF^{V600}$-mutation status in tumor tissue or plasma will be entered in the CRF.

In Phase 2, blood samples or tumor tissue will also be tested to confirm eligibility. Assessment of mutation status will first be performed using plasma ctDNA. In the event that a plasma ctDNA result cannot be interpreted, reflex testing of the tumor tissue described in Section 8.8 will be performed. In addition, tumor tissue collected after the participant was diagnosed with metastatic disease is preferred. The tumor tissue sample must not be from locations that were previously irradiated.

The blood sample collected to confirm eligibility may also be used for future development of a medical device (companion diagnostic [CDx]) that would be used to select future patients for treatment with encorafenib, binimetinib, and sasanlimab based on their $BRAF^{V600}$ mutation status.

12.8.5. Patient Reported Outcomes

PROs will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[35] and its corresponding module for lung cancer (EORTC QLQ-LC13).[36] The questionnaires will be administered at the time points described in the SoA. The questionnaires should be completed prior to any other study or medical procedure.

The EORTC QLQ-C30 is a well-known, validated and self-administered PRO questionnaire (Aaronson 1993). 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.[36] 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.

12.9. Statistical Considerations for Sub-Study A

See Section 9 for master protocol statistical considerations and sub-study specifics below.

12.9.1. Estimands and Statistical Hypotheses

12.9.1.1. Estimands

Refer to Section 12.3 for details of estimands.

12.9.1.2. Statistical Consideration for Phase 1b

The Phase 1B will utilize a Bayesian logistic regression model (BLRM) for dose finding as follows:

Identification of a recommended dose

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.[37]

Triplet combination model

For the triplet combination of encorafenib, binimetinib, and sasanlimab, the Bayesian model[37] consists of 7 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 2/3 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 Section 12.10.6.

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. 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.[37-39] 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 Section 12.10.6.

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 Section 12.10.6).

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.

12.9.1.3. Sample Size Determination

The total sample size is estimated to be approximately 80 participants for the Sub-Study A Phase 1b/2.

12.9.1.3.1. Phase 1b Dose Finding

Approximately 9-18 participants will be enrolled in the Phase 1b part. However, the total number of participants will depend on the number of dose levels needed to determine the MTD/RP2D of each combination and the number of participants evaluable for DLT at each dose level.

Beginning with the first dose level, participants will be enrolled, treated, and monitored in cohorts of 3-6 participants during the 28-day DLT evaluation period (Cycle 1). A minimum of 9 participants and up to approximately 18 participants will be enrolled to evaluate DLTs during the first cycle of treatment.

12.9.1.3.2. Phase 2 Dose Expansion

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 ORR is at least 55% (durable ORR $\geq$55%).

At the end of Phase 2:

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

12.9.1.4. Analysis Set

Refer to Section 9.3 for analysis sets.

12.9.1.5. General Considerations

12.9.1.5.1. Primary Endpoints

Phase 1b

The primary safety endpoint in Phase 1b is DLTs. Refer to Section 9.4.2.

The occurrence of DLTs and AEs constituting DLTs will be summarized for participants in the Phase 1b part as described in Section 12.3.

Phase 2

The primary efficacy endpoint in the Phase 2 part is Durable OR. Refer to Section 12.3.

Durable ORR will be calculated along with the 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.

12.9.1.5.2. Secondary Endpoints

12.9.1.5.2.1. Efficacy Analyses

Additional efficacy endpoints, durable OR (Phase 1b; refer to Section 12.9.1.5.1), 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 a 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. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment.

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

- DR is defined for participants with confirmed objective response (CR or PR) as the time from the first documentation of OR to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. The censoring rules for DR are as described below for PFS but participants will not be censored in the analysis of DR due to no adequate baseline assessment as only participants with OR are included in the analysis of DR.

- 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. 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 new anti-cancer treatment prior to an event, 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 any adequate post-baseline tumor assessments per RECIST v1.1 will be censored on the date of first dose unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

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

TTR will be summarized using simple descriptive statistics (eg, median and range). OR will be summarized as the proportion of participants in the analysis population with OR and corresponding 2-sided 95% CI using the Clopper-Pearson method. DR, PFS, and OS will be analyzed using Kaplan-Meier methods. Point estimates will be presented with 95% CIs.

12.9.1.5.2.2. Safety Analyses

For Phase 1b primary safety analysis, refer to Section 12.3 for DLT.

For Phase 1b and Phase 2 secondary safety analyses, refer to Sections 9.4.3.2 and 9.4.5.

12.9.1.5.2.3. PK Analyses

Refer to master protocol Section 9.4.3.3 for the analysis of PK endpoints for sasanlimab.

Trough concentrations for encorafenib, binimetinib 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 cohort/dose and cycle/ day. Exclusions or separate summaries for dose modifications and concomitant medications may be considered in data summaries.

Dose-normalized PK parameters (C_{trough}-DN) may be reported as appropriate.

12.9.1.5.2.4. Immunogenicity Analyses

Refer to master protocol Section 9.4.3.4 for the analysis of immunogenicity endpoint.

12.9.1.5.2.5. Biomarker Analyses

Refer to master protocol Section 9.4.4.1 for the analysis of biomarker endpoints.

12.9.1.5.2.6. Patient Reported Outcomes Analyses

The EORTC QLQ-C30 and EORTC QLQ LC13 will be scored according to its user guide/scoring manual.[40]

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 for each of the total and subscales 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.

12.9.1.5.3. Exploratory Endpoints

Refer to Section 9.4.4 for biomarker exploratory endpoints.

Depth of response is defined as a reduction in tumor burden in target lesions. Summary statistics for depth of response (n, %) will be determined and further described in the SAP.

12.9.1.5.4. Interim Analysis

A futility analysis based on ORR will be performed 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.

12.10. Supporting Documentation and Operational Considerations for Sub-Study A

12.10.1. Clinical Laboratory Tests for Sub-Study A

In addition to the clinical laboratory tests required in Master Protocol Section 10.2, the tests in Table 11 will be required for participants in Sub-Study A:

Table 11. Clinical Laboratory Tests Added for Sub-Study A

Hematology	Chemistry	Urinalysis
• Hematocrit • RBC	• CK (If total CK ≥ 3 × ULN, then measure isoenzymes, serum creatinine and myoglobin in blood weekly) • Direct bilirubin if total bilirubin values are above ULN	• Appearance • Color • Specific gravity • pH • Glucose • Ketones • Nitrite • Leukocytes • Microscopic analysis (Reflex Testing)[a]

a. Only if urine dipstick is positive for nitrites or leukocytes.

12.10.2. Contraceptive Guidance for Sub-Study A

On the basis of the mechanism of action of sasanlimab and data from approved drugs of the same class, sasanlimab may cause a risk for severe manifestations of developmental toxicity in humans; studies to evaluate the development toxicity of sasanlimab have not been conducted. Therefore, the use of a highly effective method of contraception is required

12.10.2.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 6 months after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

  PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 12.10.2.4).

12.10.2.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 12.10.2.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 6 months after the last dose of study intervention, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If the chosen highly effective method is a hormonal method, then the use of at least 1 form of non-hormonal contraception is required (see Section 12.10.2.4).

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

12.10.2.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

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

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
     - Female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.10.2.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation*.
2. Intrauterine device.
3. Intrauterine hormone-releasing system*.
4. Bilateral tubal occlusion.
5. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation*:
    - Oral;
    - Intravaginal;
    - Transdermal.
2. Progestogen-only hormone contraception associated with inhibition of ovulation*:
    - Oral;
    - Injectable.
3. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

*There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for females of childbearing potential. One of the following acceptable barrier methods must be used in addition to any of the hormonal highly effective methods listed above:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

12.10.3. Examples of Strong and Moderate CYP3A4 Inhibitors

Refer to Section 10.13.

12.10.4. Recommended Dose Modifications for Encorafenib-related* Adverse Events and Overlapping Toxicities with Sasanlimab**

Severity of Adverse Event	Dose Modifications
New Primary Malignancies	
RAS mutation-positive malignancies	Permanently discontinue encorafenib and binimetinib.
Uveitis	
Grade 1-3	Consult ophthalmologist. Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics as appropriate. If considered to be immune-related AE, • Grade 1: continue sasanlimab • Grade 2: hold sasanlimab with treatment guided by ophthalmologist with or without systemic corticosteroids • Grade 3: permanently discontinue sasanlimab with treatment guided by ophthalmologist on systemic corticosteroids. If Grade 1 or 2 uveitis considered to be encorafenib related and does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold encorafenib and binimetinib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue.
Grade 4	Permanently discontinue sasanlimab, encorafenib, and binimetinib.

Severity of Adverse Event	Dose Modifications
Other Eye Disorders (i.e., non-Uveitis Events)	
Grade 1–2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution. If considered irAE, refer to Uveitis management above.
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer participant to ophthalmologist within 7 days. • If resolved to Grade ≤1 in ≤21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤1 in ≤21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution. • If considered irAE, refer to Uveitis management above.
Grade 4	Permanently discontinue sasanlimab, encorafenib, and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
QTc Prolongation	
QTcF >500 msec and ≤60 msec increase from baseline	1st occurrence: • Temporarily interrupt dosing of encorafenib until QTcF <500 msec. Then resume treatment at 1 reduced dose level of encorafenib. 2nd occurrence: • Temporarily interrupt dosing of encorafenib treatment until QTcF <500 msec. Then resume treatment at 1 reduced dose level of encorafenib. 3rd occurrence: • Permanently discontinue encorafenib and binimetinib.
QTcF >500 msec and >60 msec increase from baseline	Permanently discontinue encorafenib and binimetinib.
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain encorafenib dose. • If no improvement within 4 weeks, withhold encorafenib until improved to Grade 0-1 or

Severity of Adverse Event	Dose Modifications
	to pretreatment/baseline levels and then resume at the same dose. Refer to Sections 6.6 and 10.10 if considered irAE.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions in this table for guidance on encorafenib and binimetinib. Permanently discontinue sasanlimab. See Sections 6.6 and 10.10 for irAE.
Dermatologic (Except Palmar-plantar Erythrodysesthesia Syndrome)	
Grade 2	If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent. Refer to Sections 6.6 and 10.10 if considered irAE.
Grade 3	Withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent. Refer to Sections 6.6 and 10.10 if considered irAE.
Grade 4	Permanently discontinue sasanlimab, encorafenib, and binimetinib. Refer to Sections 6.6 and 10.10 if considered irAE.
Hand-foot Skin Reaction (HFSR)/Palmar-plantar Erythrodysesthesia Syndrome (Dose Adjustment for Encorafenib ONLY)	
Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications.
Grade 2	1st occurrence: • Maintain dose of encorafenib and HFSR should be closely monitored. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. • If no improvement ≤14 days, interrupt dosing of encorafenib until resolved to Grade ≤1. Resume treatment with encorafenib at current dose level. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications.

Severity of Adverse Event	Dose Modifications
	Additional occurrence: • Treatment with encorafenib may be maintained or interrupted based upon the investigator's discretion. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. If interrupted dosing of encorafenib per investigator's judgment, interrupt until resolved to Grade ≤1. Resume treatment with encorafenib at the same dose level or 1 reduced dose level based upon the investigator's discretion.
Grade 3	1st or 2nd occurrence: • Interrupt dosing of encorafenib until resolved to Grade ≤1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the participant weekly. Then resume treatment at 1 reduced dose level of encorafenib. • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. >3rd occurrence: • Interrupt dosing of encorafenib until resolved to Grade ≤1, decision to resume treatment with encorafenib at 1 reduced dose level or permanently discontinue encorafenib should be based upon the investigator's discretion.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤1. Resume treatment at 1 reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).

Severity of Adverse Event	Dose Modifications
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Adverse Reactions (including renal, hemorrhage)	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue encorafenib and binimetinib.
First occurrence of any Grade 4	Permanently discontinue or withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue encorafenib and binimetinib.
Recurrent Grade 3	Consider permanently discontinuing encorafenib and binimetinib.
Recurrent Grade 4	Permanently discontinue encorafenib and binimetinib.

*For adverse events that may be related to both encorafenib and binimetinib, guidance is provided for the other agent also.

** Refer to Section 12.6.6 for management of potential overlapping toxicities. Any adverse event suspected to be immune-related should be managed accordingly as in Sections 6.6 and 10.10. Consult appropriate specialist as indicated.

12.10.5. Recommended Dose Modifications for Binimetinib-related* Adverse Events and Overlapping Toxicities with Sasanlimab**

Severity of Adverse Event	Dose Modifications
Cardiomyopathy	
Asymptomatic, absolute decrease in LVEF of >10% from baseline that is also below the LLN	Withhold binimetinib for up to 4 weeks, evaluate LVEF every 2 weeks. Resume binimetinib at a reduced dose if the following are present: • LVEF is at or above the LLN and • Absolute decrease from baseline is 10% or less and • Participant is asymptomatic. If LVEF does not recover within 4 weeks permanently discontinue binimetinib. Consult cardiologist to rule out immune-related myocarditis, see Section 10.10.
Grade 3-4 (Symptomatic congestive heart failure or absolute decrease in LVEF of >20% from baseline that is also below LLN)	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks. Consult cardiologist to rule out immune-related myocarditis, see Section 10.10.
Venous Thromboembolism	
Uncomplicated DVT or PE	Withhold binimetinib. • If improves to Grade 0-1, resume at a reduced dose. • If no improvement, permanently discontinue binimetinib.
Life threatening PE	Permanently discontinue binimetinib.
Serous Retinopathy	
Symptomatic serous retinopathy/ Retinal pigment epithelial detachments	Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume at the same dose. • If not improved, resume at a lower dose level or permanently discontinue binimetinib.
Retinal Vein Occlusion (RVO)	
Any Grade	Permanently discontinue binimetinib.
Uveitis	
Grade 1-3	Consult ophthalmologist. Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics as appropriate. If considered to be immune-related AE,

Severity of Adverse Event	Dose Modifications
	Grade 1: continue sasanlimab. Grade 2: hold sasanlimab with treatment guided by ophthalmologist with or without systemic corticosteroids. Grade 3: permanently discontinue sasanlimab with treatment guided by ophthalmologist on systemic corticosteroids. If Grade 1 or 2 considered to be binimetinib related and does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold binimetinib and encorafenib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue binimetinib.
Grade 4	Permanently discontinue binimetinib and sasanlimab.
Other Eye Disorders (ie, Non-retinal Events, non-Uveitis Events	
Grade 1-2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution. If considered irAE, refer to Uveitis management above.
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer participant to ophthalmologist within 7 days. • If resolved to Grade ≤1 in ≤21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤1 in ≤21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution. If considered irAE, refer to Uveitis management above.
Grade 4	Permanently discontinue sasanlimab, encorafenib, and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
Interstitial Lung Disease	
Grade 1	Consider withholding sasanlimab if considered irAE, see Section 10.10.
Grade 2	Withhold binimetinib for up to 4 weeks.

Severity of Adverse Event	Dose Modifications
	• If improved to Grade 0-1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue. Withhold Sasanlimab if considered irAE, see Section 10.10.
Grade 3 or Grade 4	Permanently discontinue binimetinib and sasanlimab. See Section 10.10 if considered irAE.
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain binimetinib dose. • If no improvement within 2 weeks, withhold binimetinib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose. Refer to Sections 6.6 and 10.10 if considered irAE.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions in this table for guidance on encorafenib and binimetinib. Permanently discontinue sasanlimab. See Sections 6.6 and 10.10 for irAE.
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations	
Grade 4 asymptomatic CPK elevation or Any Grade CPK elevation with symptoms or with renal impairment	Withhold binimetinib dose for up to 4 weeks. • If improved to Grade 0-1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib.
Dermatologic	
Grade 2	If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 3	Withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 4	Permanently discontinue binimetinib and encorafenib.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.

Severity of Adverse Event	Dose Modifications
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤1. Then resume treatment at 1 reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice). If unresolved permanently discontinue binimetinib and encorafenib.
Grade 4	Permanently discontinue binimetinib and encorafenib.
Other Adverse Reactions. Refer to Sections 6.6 and 10.10 if considered irAE	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue binimetinib and encorafenib.
First occurrence of any Grade 4	Permanently discontinue or withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue binimetinib and encorafenib.
Recurrent Grade 3	Consider permanently discontinuing binimetinib and encorafenib.
Recurrent Grade 4	Permanently discontinue binimetinib and encorafenib.

*For adverse events that may be related to both binimetinib and encorafenib, guidance is provided for the other agent also.

** Refer to Section 12.6.6 for management of potential overlapping toxicities. Any adverse event suspected to be immune-related should be managed accordingly as in Sections 6.6 and 10.10. Consult appropriate specialist as indicated.

12.10.6. 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:

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

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

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 12 are used to derive the prior of the single agent logistic parameters for encorafenib.

Table 12. 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 13).[37]

Table 13. 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 14 are used to derive the prior of the single agent logistic parameters for binimetinib.

Table 14. 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 15. 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)

Table 15. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Binimetinib Model Parameters

Parameter	Prior Distribution

(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 16 are used to derive the prior of the single agent logistic parameters for sasanlimab.

Table 16. 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 17).[37]

Table 17. 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 18.

Table 18. Prior Distribution for the Model Parameters

Parameter	Mean	Standard Deviations	Correlation
Encorafenib single agent parameters: BVN MAP Prior			
$\left(\log(\alpha_1), \log(\beta_1)\right)$	-0.904, 0.268	0.822, 0.630	0.117
Binimetinib single agent parameters: BVN MAP Prior			
$\left(\log(\alpha_2), \log(\beta_2)\right)$	-2.785, 0.376	0.596, 0.860	-0.330
Sasanlimab single agent parameters: BVN MAP Prior			
$\left(\log(\alpha_3), \log(\beta_3)\right)$	-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 19, 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 19. 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 20 shows data scenarios for the triplet combination and the corresponding recommendations for the next dose.

Table 20. 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

Table 20. 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)		

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 21). Scenario 1 represents the case when the distribution of DLT coincides with prior, ie, 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 21. 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%, ie, 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 22. 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 22. 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

Table 22. Combination A: Operating Characteristics

Scenarios	Participant allocation (%)			Pr (declare MTD) (%)			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
With under dose and target dose	64.0	0	35.9	96.1	0	0	3.9	8.8

13. APPENDIX B: SUB-STUDY B: SASANLIMAB + AXITINIB + SEA-TGT

13.1. Schedule of Activities (SoA): Sub-Study B

The SoA table provides an overview of the sub-study visits and procedures. Refer to Section 8 of the master protocol and Section 13.8 of this sub-study appendix for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule unplanned visits in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant, or if otherwise clinically indicated.

Table 23. Schedule of Activities Sub-Study B Phase 1b & Phase 2

Visit Identifier[a]	Pre-Screening[b]	Screening[b] (≤28 days prior to first dose)	Treatment Period									Follow-Up[d]		
			Cycle 1 (Days 1 to 21)		Cycle 2 (Days 1 to 21)		Cycles 3 & 4 (Days 1 to 21)	Cycle 5 (Days 1 to 21)		Cycles ≥ 6 (Days 1 to 21)				
			Day 1	Day 8	Day 1	Day 8	Day 1	Day 1	Day 8	Day 1	EOT[c]	Day 30[d]	Days 60, 90, & 180[d]	Survival[d]
Visit Window				±1	±2	±2	±2	±2	±2	±2		±7	±7	±7
Informed consent[e]	X	X												
Eligibility review	X	X	X											
Tumor and medical history[f]		X												
Substance and tobacco use		X									X			
Physical examination[g]		X	X	X	X		X	X	X	X	X			
Height		X												
Weight		X	X		X		X	X		X	X			
In-clinic Vital signs[h]		X	X	X	X		X	X	X	X	X	X		
Home Blood Pressure Monitoring[i]			(continuous starting C1D1)											
ECHO/MUGA[j]		X									X			
ECOG performance status[k]		X	X											
Triplicate 12-lead ECG[l]			X											
Single 12-lead ECG[l]		X		X	X		X	X		X	X	X		
Laboratory Assessments of Hematology and Blood Chemistry[m]		X	X	X	X	X	X	X	X	X	X	X		
Coagulation[m]		X	X		X		X	X		X	X	X		
Urinalysis[n]		X	X	X	X	X	X	X	X	X	X	X		
Pregnancy test[o]		X	X		X		X	X		X	X	X	X	
Hepatitis B, C tests[p]		X												
Endocrinology tests[m]		X			Every 4 cycles starting at C4D1									
Allocation to study intervention[q]			X											
Dispensing of axitinib			X		X		X	X		X				

Table 23. Schedule of Activities Sub-Study B Phase 1b & Phase 2

Visit Identifier[a]	Pre-Screening[b]	Screening[b] (≤28 days prior to first dose)	Treatment Period									Follow-Up[d]		
			Cycle 1 (Days 1 to 21)		Cycle 2 (Days 1 to 21)		Cycles 3 & 4 (Days 1 to 21)	Cycle 5 (Days 1 to 21)		Cycles ≥ 6 (Days 1 to 21)				
			Day 1	Day 8	Day 1	Day 8	Day 1	Day 1	Day 8	Day 1	EOT[c]	Day 30[d]	Days 60, 90, & 180[d]	Survival[d]
Administration of study treatment sasanlimab[r]			X		X		X	X		X				
Administration of study treatment SEA-TGT[s]			X		X		X	X		X				
Administration of study treatment axitinib[t]			Continuous BID starting C1D1											
Local site injection tolerability assessment[u]			X		X		X	X		X				
Tumor assessment[v]		X	Every 6 wks (±7 days) from C1D1 for the first 12 months, then every 12 wks (±7 days) thereafter according to calendar, regardless of treatment delays and until progressive disease assessed by investigator using RECIST v1.1 or start of new anti-cancer therapy											
Nonserious and serious adverse events[w]		X	→	→	→	→	→	→	→	→	→	→	→	→
Prior and Concomitant medication/surgery/ radiation & non-drug supportive interventions[x]		X	X	X	X		X	X	X	X	X	X		
Survival & subsequent anti-cancer therapy											X	X	X	X
Contraception check[y]		X	X		X		X	X		X	X	X	X	
Remote visit						X							X	X
PK for sasanlimab[z]			X	X	X		X	X	X	X (C7, C10, C13, C16, then every 6 cycles)				

Table 23. Schedule of Activities Sub-Study B Phase 1b & Phase 2

Visit Identifier[a]	Pre-Screening[b]	Screening[b] (≤28 days prior to first dose)	Treatment Period									Follow-Up[d]		
			Cycle 1 (Days 1 to 21)		Cycle 2 (Days 1 to 21)		Cycles 3 & 4 (Days 1 to 21)	Cycle 5 (Days 1 to 21)		Cycles ≥ 6 (Days 1 to 21)				
			Day 1	Day 8	Day 1	Day 8	Day 1	Day 1	Day 8	Day 1	EOT[c]	Day 30[d]	Days 60, 90, & 180[d]	Survival[d]
PK for SEA-TGT[aa]			X	X	X		X	X	X	X (C7, C10, C13, C16, then every 6 cycles)				
PK for axitinib[bb]			X	X	X		X	X	X					
Baseline tumor biospecimen[cc]		X												
Biobanked biospecimen for genetics[dd]			X											
Blood for cell-free (cf) DNA analysis[ee]			X		X		X (C4 only)				X			
Blood for specified genetic research[ff]		X	X	X	X									
Blood for T-Cell Receptor (TCR) analysis[ii]		X	X	X	X									
Immunogenicity for sasanlimab[jj]			X		X		X	X		X (C7, C10, C13, C16 and then every 6 cycles)	X			
Immunogenicity for SEA-TGT[kk]			X		X		X	X		X (C7, C10, C13, C16 and then every 6 cycles)	X			

a. **Day** relative to start of study intervention (Day 1).

Table 23. Schedule of Activities Sub-Study B Phase 1b & Phase 2

Visit Identifier[a]	Pre-Screening[b]	Screening[b] (≤28 days prior to first dose)	Treatment Period									Follow-Up[d]		
			Cycle 1 (Days 1 to 21)		Cycle 2 (Days 1 to 21)		Cycles 3 & 4 (Days 1 to 21)	Cycle 5 (Days 1 to 21)		Cycles ≥ 6 (Days 1 to 21)				
			Day 1	Day 8	Day 1	Day 8	Day 1	Day 1	Day 8	Day 1	EOT[c]	Day 30[d]	Days 60, 90, & 180[d]	Survival[d]

b. The **Pre-Screening** period is optional and allows local PD-L1 and genetic testing to start after completion of the pre-screening consent, and before the Screening period. **Screening:** To be performed within 28 days prior to first dose. Visit may be conducted over multiple days.
c. **End of Treatment (EOT) Visit:** Conducted at the visit that the participant is discontinued from study treatment or no longer than 1 week after the decision to discontinue the participant from study treatment. See Section 8.11.
d. **Follow-up:** The initial safety follow-up visit will be conducted at the study clinic 30 days after the last dose of study intervention. The 60, 90, and 180-day follow-up may be conducted by remote contact (eg. telephone). See Section 8.2.8. **Survival Follow-Up:** Only for Phase 2. Participants will be contacted every 12 weeks (±7 days) after the last clinic visit until death, lost-to-follow-up, study termination, end of study, or withdrawal of consent. See Section 8.1.3.
e. **Informed Consent:** Must be obtained prior to undergoing any study specific procedures. May be obtained more than 28 days prior to first dose.
f. **Tumor History:** Includes history of disease under study including details of primary diagnosis, treatment history and staging. **Medical History:** Includes history other than the cancer under study. Abnormalities observed during screening are to be considered as medical history.
g. **Physical examination (PE):** See Section 8.2.1.
h. **Vital Signs:** Includes temperature, blood pressure, and pulse rate. On Day 1 of each cycle, vital signs are to be measured within 60 minutes prior to administration of any study intervention (pre-dose), at the completion of the SEA-TGT infusion, and at the completion of the 2-hour-post-dose observation period (on Cycles 1, 2, 3 only).
i. **Home BP monitoring:** Participants will monitor their BP at least twice daily (before taking each dose of axitinib) and record the results in the diary. See Section 13.8.2.1.
j. **ECHO/MUGA:** The same modality used during screening is to be used for any subsequent assessments. Assessment will also be performed if a participant experiences an AE which may be related to cardiac dysfunction in the opinion of the investigator, or as otherwise clinically indicated. See Section 13.8.2.2.
k. **Eastern Cooperative Oncology Group (ECOG) Performance Status:** See Section 8.2.6.
l. **Triplicate and Single 12 Lead electrocardiogram (ECG):** When triplicate ECG is requested, 3 serial 12-lead ECGs will be conducted within approximately 5-10 minutes total time. Triplicate ECGs on C1D1 will be collected prior to administration of any study intervention. For remaining timepoints, single ECG will be collected prior to administration of study intervention. When coinciding with blood sample draws for PK, ECG assessment is to be performed prior to blood sample collection, such that the blood sample is collected at the nominal time.
m. **Hematology, Blood Chemistry, Endocrinology, and Coagulation tests:** See Sections 10.2 and 13.10.1 for lists of Laboratory Tests. Not necessary to repeat on C1D1 if performed within 7 days prior to C1D1 as part of Screening. Subsequent assessments must be performed within 72 hours prior to the scheduled visit. Hematology and chemistry assessments on C2D8 may be drawn at a lab local to the participant and do not require on-site visit. See Section 10.2 for more details about clinical lab assessments.

Table 23. Schedule of Activities Sub-Study B Phase 1b & Phase 2

Visit Identifier[a]	Pre-Screening[b]	Screening[b] (≤28 days prior to first dose)	Treatment Period									Follow-Up[d]		
			Cycle 1 (Days 1 to 21)		Cycle 2 (Days 1 to 21)		Cycles 3 & 4 (Days 1 to 21)	Cycle 5 (Days 1 to 21)		Cycles ≥ 6 (Days 1 to 21)				
			Day 1	Day 8	Day 1	Day 8	Day 1	Day 1	Day 8	Day 1	EOT[c]	Day 30[d]	Days 60, 90, & 180[d]	Survival[d]

n. **Urinalysis:** Dipstick is acceptable. No need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. Urinalysis assessments on C2D8 may be drawn at a lab local to the participant and do not require an on-site visit. See Section 10.2 for urinalysis details.

o. **Pregnancy Test (Serum/Urine):** For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy, once at screening and once at the C1D1 visit before dosing. Participants with a confirmed positive pregnancy test(s) must not be dosed. Pregnancy tests will also be routinely performed throughout the study as per the SOA and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be performed if requested by IRB/EC or if required by local regulations. At the 60, 90, and 180-day remote follow-up visits, pregnancy tests may be conducted via home kits.

p. **Hepatitis B, C:** In the case of apparent ongoing HBV or HCV infection, reflex serum viral load testing will be performed.

q. **Allocation:** The participant allocation number will be assigned using an IRT system. Participants can be allocated in IRT no more than 3 days prior to dosing. See Section 6.3.1 for more details.

r. **Study Treatment sasanlimab:** Will be administered [redacted] (maximum volume per injection is 2 mL). Sasanlimab should be administered first, followed by axitinib, and then SEA-TGT. See Section 6.1.1.

s. **Study Treatment SEA-TGT:** Will be administered once every 21 days as an IV infusion in a stepwise manner. See Section 13.6.1.2.

t. **Study Treatment axitinib:** Twice daily oral administration. See Section 13.6.1.1.

u. **Local Site Injection Tolerability Assessment:** See Section 8.2.7.

v. **Tumor Assessments:** Tumor response assessments will be determined in accordance with RECIST v1.1. See Section 8.1.1.

w. **Nonserious and Serious AE Assessments:** AEs and SAEs are documented and recorded at each visit using NCI CTCAE version 5.0. See Section 8.3.

x. **Concomitant Medications and Non-Drug Supportive Interventions:** Includes supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions). Reporting period for concomitant medications for AEs and SAEs are to follow respective AE and SAE reporting period. See Sections 6.5 and 13.6.5.

y. **Contraceptive Check:** Male participants who are able to father children and female participants who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected methods of contraception throughout the study and continue for 6 months after the last dose. The investigator or his or her designee will discuss with the participant the need to use the appropriate contraception methods consistently and correctly and document such conversation in the participant's chart. The investigator or his or her designee will instruct the participant to call immediately if the selected contraception methods are discontinued, or if pregnancy is known or suspected in the participant or participant's partner. See Section 13.10.2.

z. **PK for sasanlimab:** One 3-mL blood sample will be collected for sasanlimab PK on each day indicated in the SoA. All samples taken on Day 1 of a cycle will be collected within 6 hours prior to dosing of sasanlimab. The PK sample may be collected anytime during the visit on sampling days that are not Day 1 of a cycle.

Table 23. Schedule of Activities Sub-Study B Phase 1b & Phase 2

Visit Identifier[a]	Pre-Screening[b]	Screening[b] (≤28 days prior to first dose)	Treatment Period									Follow-Up[d]		
			Cycle 1 (Days 1 to 21)		Cycle 2 (Days 1 to 21)		Cycles 3 & 4 (Days 1 to 21)	Cycle 5 (Days 1 to 21)		Cycles ≥ 6 (Days 1 to 21)				
			Day 1	Day 8	Day 1	Day 8	Day 1	Day 1	Day 8	Day 1	EOT[c]	Day 30[d]	Days 60, 90, & 180[d]	Survival[d]

aa. **PK for SEA-TGT:** One 3-mL blood sample will be collected for SEA-TGT PK on each day indicated in the SoA. All samples taken on Day 1 of a Cycle will be collected at predose (within 6 hours prior to dosing of SEA-TGT) and End of Infusion (EOI), within 15 minutes following infusion stop. The PK sample may be collected anytime during the visit on sampling days that are not Day 1 of a cycle.

bb. **PK for axitinib:** One 3-mL blood sample will be collected for axitinib PK on each day indicated in the SoA. Samples on Day 1 of Cycle 1 and Cycle 5 will be collected at predose (within 2 hours prior to axitinib dose) and 3 hours post-axitinib dose. The PK sample will be collected predose (within 2 hours prior to axitinib dose) on all other sampling days.

cc. **Baseline tumor biospecimen: Phase 2 only.** A tumor tissue sample (primary or metastatic, archival or new) will be obtained by a procedure performed prior to Cycle 1 Day 1, except as approved by the Sponsor. The sample will be used to confirm PD-L1 status at a central lab (Section 8.8.2), and may also be used for specified analyses (Sections 8.7.1 and 8.8.2) or exploratory biomarker analysis (Section 8.8).

dd. **Banked biospecimen for genetics:** A 4-mL blood sample will be collected on Cycle 1 Day 1 prior to dosing with any study intervention and retained in a biobank for possible assessments of genes and other analytes (eg, proteins, RNA, nondrug metabolites), unless prohibited by local regulations or by decision of the institutional review board or ethics committee (Section 8.7.2).

ee. **Blood for cell-free (cf) DNA Analysis:** A 20-mL blood sample for preparation of plasma will be collected prior to dosing with any study intervention and at Day 1 of Cycles 2 and 4 for exploratory analyses as described in Section 8.7.1.

ff. **Blood for specified genetic research:** A 4-mL whole blood sample will be collected prior to dosing with any study intervention and at Cycle 1 Day 1 (pre-dose), Cycle 1 Day 8, and at Cycle 2 Day 1 (pre-dose) for exploratory genetic and epigenetic analyses as described in Section 8.7.1.

gg. NA.

hh. NA.

ii. **Blood for T-Cell Receptor (TCR) Analysis:** A 6-mL whole blood sample will be collected into a tube optimized for DNA preservation prior to dosing with any study intervention and at Cycle 1 Day 1 (pre-dose), Cycle 1 Day 8, and at Cycle 2 Day 1 (pre-dose) (Section 8.7.1).

jj. **Blood for sasanlimab Immunogenicity (anti-drug antibody [ADA] and possibly neutralizing antibodies [NAb]) Testing:** All samples (6 mL each) taken on Day 1 of a cycle will be taken prior to dosing with any study intervention and within 6 hours prior to sasanlimab dosing. See Section 8.9.

kk. **Blood for SEA-TGT Immunogenicity (anti-drug antibody [ADA] and possibly neutralizing antibodies [NAb]) Testing:** All samples (5- mL each) taken on Day 1 of a cycle will be taken prior to dosing with any study intervention and within 6 hours prior to SEA-TGT dosing. See Section 8.9.

13.2. Introduction for Sub-Study B

13.2.1. Study Rationale

See master protocol Section 2.1 for the Umbrella Study rationale and Section 13.4.3 for the Sub-Study B rationale.

13.2.2. Background

See the master protocol Introduction (Section 2) for background on sasanlimab.

13.2.2.1. Background for Axitinib

Axitinib (INLYTA®) is an oral, small molecule, TKI selective for VEGFRs 1, 2 and 3 and is approved multinationally for the treatment of advanced RCC after failure of one prior systemic therapy (actual indication varies according to region/country) and in combination with avelumab or pembrolizumab for the 1L treatment of patients with advanced RCC.

Axitinib is an ATP-competitive inhibitor that binds to the unphosphorylated (non-activated) "DFG-out" conformation of the catalytic domain of a receptor tyrosine kinase. In enzymatic assays, axitinib was found to be highly potent (Ki = 28 picomolar) against the kinase activity of juxta-membrane (JM) domain containing human VEGFR 2 recombinant protein.[41] In additional kinase assays, axitinib showed potent and ATP-competitive inhibition of the VEGFRs 1, 2, and 3 and PDGFR-β, but not other closely-related family kinases. Receptor binding studies and cell-based assays, confirmed that axitinib is a potent and selective inhibitor of VEGFRs 1, 2, and 3. Axitinib was shown to have antiangiogenic activity in a number of models including spontaneous pancreatic islet-cell tumors of RIP-TAG-2 transgenic mice model and demonstrated antitumor efficacy including marked cytoreductive antitumor activity, in multiple tumor models implanted in athymic mice.

13.2.2.2. Background for SEA-TGT

TIGIT is an adaptive checkpoint receptor expressed on several subsets of T-cells. TIGIT engages its ligands in the tumor microenvironment and decreases T-cell activity. SEA-TGT blocks this interaction and relieves TIGIT-mediated suppression of antitumor CD8+ T-cells, unleashing these cells against the tumor. Furthermore, because SEA-TGT is non-fucosylated, it binds FcγRIII with high affinity, resulting in depletion of cells expressing TIGIT, such as T regulatory cells (Tregs). Enhanced FcγRIII binding also augments activation of memory T-cells and generation of new antigen-specific T-cell responses. These activities increase the antitumor activity of SEA-TGT.

SEA-TGT may be unique in its ability to elicit effector T-cell responses; SEA-TGT treatment of PBMC cultures resulted in activation of innate immune cells and cytokine production. This suggests that SEA-TGT may activate both adaptive and innate arms of the immune system. These in vitro results translated to in vivo antitumor activity in the CT26 colon cancer model, where SEA-TGT treatment decreased intratumoral Tregs, increased total intratumoral CD8+ effector memory T-cells, and resulted in curative antitumor responses. These pharmacodynamic changes and antitumor responses were associated with the generation of antigen-specific immunity and

long-term memory T-cell responses, resulting in complete tumor rejection upon re-challenge. Furthermore, SEA-TGT treatment in the MC38 (colon carcinoma) and A20 (lymphoma) syngeneic tumor models resulted in tumor growth delay and complete responses (CRs) in both models.

Collectively, these data demonstrate the antitumor therapeutic potential of SEA-TGT and suggest activity comes both from reduction of Tregs and amplification of naïve and memory T-cell responses.

13.2.2.3. Clinical Overview of Sub-Study B Investigational Products

See the master protocol Introduction (Section 2.2.2) for clinical overview of sasanlimab.

13.2.2.3.1. Clinical Overview of Axitinib

- The efficacy and safety of single-agent axitinib were evaluated in a Phase II open-label study (NCT00094094; study A4061011) in 32 patients with advanced NSCLC, with (n=23) and without (n=9) prior therapy.[42]
    - The most common (≥20%) treatment-related AEs were fatigue, anorexia, diarrhea, nausea, hoarseness, hypertension, and arthralgia; most were Grade ≤2 in severity. Grade ≥3 treatment related AEs included fatigue (n=7), hypertension (n=3), and hyponatremia (n=3); other grade ≥3 treatment related AEs occurred in 1 participant each.
    - Three patients had confirmed PR (ORR =9%); disease control rate (PR + stable disease) was 41%. Median duration of response was 8.3 months (95% CI, 5.9,10.6). Median PFS was 4.9 months overall (95% CI, 3.6,7.0). Median OS was 14.8 months (95% CI, 10.7,not estimable).
- The efficacy and safety of axitinib in combination with avelumab were demonstrated in the Javelin Renal 101 study (NCT02684006; B9991003) in which 886 patients with untreated advanced RCC were randomly assigned to receive either avelumab plus axitinib (N = 442) or sunitinib (N = 444).[43]
    - The most common (≥20%) adverse reactions in patients receiving axitinib in combination with avelumab were diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache. Serious adverse reactions occurred in 35% of patients receiving axitinib in combination with avelumab and those that occurred in ≥1% of patients included diarrhea (2.5%), dyspnea (1.8%), hepatotoxicity (1.8%), venous thromboembolic disease (1.6%), acute kidney injury (1.4%), and pneumonia (1.2%). Fatal adverse reactions occurred in 1.8% of patients receiving axitinib in combination with avelumab and included sudden cardiac death (1.2%), stroke (0.2%), myocarditis (0.2%), and necrotizing pancreatitis (0.2%).[43]

- There was a statistically significant improvement in PFS (HR=0.69; 95% CI, 0.56, 0.84) with median PFS of 13.8 months (95% CI; 11.1, not estimable) in the axitinib + avelumab group and 8.4 months (95% CI; 6.9,11.1) in the sunitinib group. The confirmed ORR was 51% (95% CI, 46.6,56.1) in the axitinib + avelumab group versus 26% (95% CI, 21.7, 30) in the sunitinib group.[43]

- The efficacy and safety of axitinib in combination with avelumab was also evaluated in the Javelin Medley VEGF study (B9991027, NCT03472560) that included 41 patients with advanced/metastatic NSCLC who had received at least 1 prior platinum-containing therapy and 20 patients with advanced/metastatic UC who were treatment naïve.[44]

  - The most common (>10%) treatment related AEs in the NSCLC cohort were hypertension (39%), hypothyroidism (29%), decreased appetite (27%), diarrhea (22%), fatigue (22%), and hand-foot syndrome (15%); and in the UC cohort were asthenia (20%), decreased appetite (15%), fatigue (15%), and hypertension (15%).[44]

  - Avelumab + axitinib showed antitumor activity in both cohorts, and tumor reduction was observed regardless of PD-L1 expression status. The confirmed ORR was 31.7% (95% CI: 18.1,48.1) in the NSCLC cohort and 10% (95% CI: 1.2,31.7) in the UC cohort (all partial responses). Median PFS was 5.5 months (95% CI: 2.5,7.0) in the NSCLC cohort and 2.3 months (95% CI: 1.8,5.6) in the UC cohort.

- The efficacy of axitinib in combination with pembrolizumab was investigated in the Keynote-426 study (NCT02853331) in 861 patients with untreated advanced RCC.[43]

  - The most common adverse reactions (≥20%) in patients receiving axitinib and pembrolizumab were diarrhea, fatigue/asthenia, hypertension, hypothyroidism, decreased appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. Serious adverse reactions occurred in 40% of patients receiving axitinib in combination with pembrolizumab and those that occurred in ≥1% of patients receiving axitinib in combination with pembrolizumab included hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%). Fatal adverse reactions occurred in 3.3% of patients receiving axitinib in combination with pembrolizumab and included 3 cases of cardiac arrest, 2 cases of pulmonary embolism and 1 case each of cardiac failure, death due to unknown cause, myasthenia gravis, myocarditis, Fournier's gangrene, plasma cell myeloma, pleural effusion, pneumonitis, and respiratory failure.[43]

  - There were statistically significant improvements in OS, PFS, and ORR in the axitinib + pembrolizumab group vs. the sunitinib group. OS at 1 year was

90% (95% CI; 86,92) in the axitinib + pembrolizumab group vs 78% (95% CI; 74,82) in the sunitinib group. Median PFS (HR=0.69; 95% CI; 0.56,0.84) was 15 months (95% CI; 12.6,17.7) vs 11 months (95% CI; 8.7,12.5), and the confirmed ORR was 59% (95% CI; 54,64) vs 36 % (95% CI; 31,40) in the axitinib + pembrolizumab group vs. the sunitinib group, respectively.[43]

See Section 13.4.3 for the rationale of combining a PD-1/PD-L1 inhibitor with a VEGR inhibitor in this study. Additional information regarding clinical safety and efficacy is presented in the IB for axitinib.[41]

13.2.2.3.2. Clinical Overview of SEA-TGT

The first-in-human study currently ongoing is a Phase 1, dose-escalation study to evaluate the safety and tolerability of SEA-TGT IV Q3W as a monotherapy and in combination with sasanlimab in participants with advanced malignancies (SGNTGT-001, NCT04254107). The monotherapy study will evaluate alternate dosing schedules, identify the maximum tolerated dose (MTD), maximum administered dose (MAD), or an alternative recommended active dose (not exceeding MTD). The SEA-TGT IV doses explored in this study are 0.01, 0.1, 0.3, 1, 3, and 6 mg/kg. Based on the multiple potential mechanisms of action, SEA-TGT may be an active therapy in a variety of malignancies. Therefore, that initial clinical study began with dose escalation in participants with selected advanced malignancies including NSCLC, gastric/gastroesophageal cancer, melanoma, classical Hodgkin lymphoma, diffuse large B-cell lymphoma, and peripheral T-cell lymphoma-NOS. Once dose escalation is completed, safety run-in cohorts will be initiated with sasanlimab. The first cohort will evaluate sasanlimab CCI + SEA-TGT at 1 dose level below the RP2D. If no DLTs are observed in the first 6 participants, 6 additional participants will receive sasanlimab + SEA-TGT at the RP2D. If no DLTs are observed in this regimen, it will be recommended for Phase 2 trials. Additional information regarding SEA-TGT is presented in the IB.[45]

As of August 04, 2021, 26 participants have been dosed. No efficacy data is available at this time. SEA-TGT monotherapy demonstrated acceptable safety and tolerability at all dose levels evaluated. The incidence of non-serious adverse events was low. The most common treatment emergent adverse events (>15% of participants) were fatigue, fever, chills, pruritus, headache, alkaline phosphatase elevation, and nausea. Among all participants enrolled across dose escalation cohorts, a single DLT of Grade 3 pruritic rash was observed in the 6 mg/kg cohort (total of 6 participants in this cohort).

No dose modifications or discontinuations due to AEs or deaths have been reported.

Overall, safety evaluation of the SEA-TGT dose escalation demonstrates a favorable benefit-risk profile in this population of patients with advanced malignancies and unmet need (preliminary data on file).

Recent safety data are available for 2 other anti-TIGIT drugs: tiragolumab and vibostolimab.

- Tiragolumab
    - In a Phase 1 study, tiragolumab was evaluated as a monotherapy (n=24) and in combination with atezolizumab (n=49) in patients with advanced solid tumors. No dose limiting toxicities were seen in the monotherapy or combination phases. The most common treatment-related AE in the monotherapy phase included fatigue (38%) and anemia (31%) in the combination group.[46]
    - In the randomized, double-blind Phase 2 CITYSCAPE study (NCT03563716), 135 patients with PD-L1-positive advanced/metastatic NSCLC were randomly assigned to receive tiragolumab + atezolizumab (n=67) or placebo + atezolizumab (n=68) in the first-line setting. Non-serious AEs that occurred in ≥20% in either group included asthenia (25% in each group), fatigue (22% in tiragolumab + atezolizumab group, 13% in placebo+ atezolizumab group), and IRRs (27% in the tiragolumab + atezolizumab group and 10% in placebo + atezolizumab group). Serious AEs that occurred in ≥2 patients in either group were influenza (2 tiragolumab + atezolizumab group and 0 in placebo + atezolizumab group), pneumonia (5 tiragolumab + atezolizumab group and 4 in placebo+ atezolizumab group), pleural effusion (4 tiragolumab + atezolizumab group and 0 in placebo + atezolizumab group), and pulmonary embolism (0 tiragolumab + atezolizumab group and 2 in placebo + atezolizumab group).[47]
- Vibostolimab
    - In a Phase 1 study, vibostolimab was evaluated as a monotherapy and in combination with pembrolizumab in various advanced solid tumors and demonstrated a manageable profile. In Part 2 of the Phase 1 study, vibostolimab was evaluated as a monotherapy (n=41) and in combination with pembrolizumab (n=38) in patients with NSCLC whose disease progressed on prior PDx therapy.[48] The most common treatment-related AEs (≥10% in either arm) were pruritus, fatigue, rash, arthralgia, and decreased appetite. Ten patients reported Grade 3-4 treatment-related AEs; the most common were lipase increase and hypertension. One patient in the vibostolimab + pembrolizumab arm died due to treatment-related pneumonitis.
    - In this same study, 41 patients with PDx-naïve NSCLC received vibostolimab + pembrolizumab. The most common (≥20%) treatment-related AEs were pruritus (34%), hypoalbuminemia (29%), and pyrexia (20%). Grade 3-4 treatment-related AEs occurred in 6 patients (15%); no deaths due to treatment-related AEs were reported.[49]

See Section 13.4.3 for the rationale of combining a PD-1/PD-L1 inhibitor with an anti-TIGIT in this study.

13.2.3. Benefit/Risk Assessment

Single-agent axitinib has demonstrated anti-tumor activity and a manageable safety profile in patients with advanced NSCLC, as described in Section 13.2.2.3.1.

Axitinib is approved in combination with either pembrolizumab or avelumab for aRCC as described in Section 13.2.2.1, and has a well-characterized safety profile, as described in Section 13.2.2.3.1. Sasanlimab is similar in mechanism of action to pembrolizumab; therefore, it is expected that sasanlimab combined with axitinib will follow a similar toxicity profile as the approved axitinib plus pembrolizumab combination. AEs with potential combinational toxicities are hepatotoxicity, hypothyroidism, diarrhea, nausea, asthenia/fatigue and decreased appetite. There is specific guidance to the investigator for dosing and concomitant therapy for participants experiencing these AEs, which are considered to be immune-related, in Section 10.10.

Other anti-TIGIT drugs, tiragolumab and vibostolimab, have been well-tolerated and efficacious as monotherapies and in combination with PD-1/PD-L1 inhibitors in first-line treatment of advanced NSCLC and PDx-refractory advanced NSCLC. The safety profile of tiragolumab in combination with atezolizumab was deemed similar to that of single-agent PD-1/PD-L1 inhibitors, while the efficacy of the combination demonstrated significant improvement in PFS and ORR over atezolizumab alone in PD-L1-positive, advanced NSCLC. The combination of vibostolimab and pembrolizumab was well-tolerated and demonstrated modest antitumor activity in PDx-refractory NSCLC, and promising antitumor activity in PDx-naïve NSCLC. See Section 13.2.2.3.2 and Section 13.4.3 for more details and references for the safety and efficacy, respectively, of these combinations. It is expected that sasanlimab combined with SEA-TGT will follow a similar toxicity profile as that of tiragolumab + atezolizumab and vibostolimab + pembrolizumab.

For the triplet combination of sasanlimab + axitinib + SEA-TGT, the safety profile has not been characterized. Study participants may experience adverse reactions that are not currently observed in the single-agent or combination profiles for each of the drugs. Such risks exist with current standard of care treatments. Despite advances in the treatment landscape for patients with advanced NSCLC without driver mutations, progression-free survival remains modest. While the introduction of immune checkpoint inhibition improved clinical outcomes compared to chemotherapy, not all patients benefit from single-agent PD-1/PD-L1 inhibitors. The combination of sasanlimab with SEA-TGT, another ICI, would theoretically introduce overlapping toxicities of some immune related AEs (irAEs) in general. The recommended irAE management guidelines are provided in Section 10.10. The recommended dose modification guidelines for toxicities due to SEA-TGT and axitinib are provided in Sections 13.10.4 and 13.10.5, respectively.

The dose modification and toxicity management guidance in this protocol is expected to mitigate the risk of these classes of toxicities, which might be increased in frequency and/or severity in this study. Further, the inclusion and exclusion criteria are intended to ensure

participants with related risk factors are not enrolled in this study, and ongoing safety monitoring will be conducted according to the SoA.

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with the combination of sasanlimab, axitinib, and SEA-TGT are justified by the anticipated benefits that may be afforded to participants with advanced NSCLC.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sasanlimab, axitinib, and SEA-TGT may be found in the IBs, which are the SRSDs for this sub-study.

13.3. Objectives, Endpoints, and Estimands for Sub-Study B

The following objectives and endpoints are specific to the Sub-Study B:

Table 24. 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**
• 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 (C_{max}, C_{trough}) of sasanlimab, axitinib, and SEA-TGT, as data permit.

Table 24. Sub-Study B Objectives and Endpoints

Objectives	Endpoints
• To evaluate the immunogenicity of sasanlimab.	• ADA (ie, incidence) against sasanlimab, as data permit.
• To evaluate the immunogenicity of SEA-TGT.	• ADA (ie, 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 (C_{max}, C_{trough}) 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

Table 24. Sub-Study B Objectives and Endpoints

Objectives	Endpoints
	tumor tissue biospecimen obtained at baseline, on treatment or at end-of-study.

Estimands

This section defines the estimands associated with the primary endpoints of the sub-study.

The primary endpoint definitions and the observations that will be considered in the derivation of the endpoints are described or referenced below.

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.

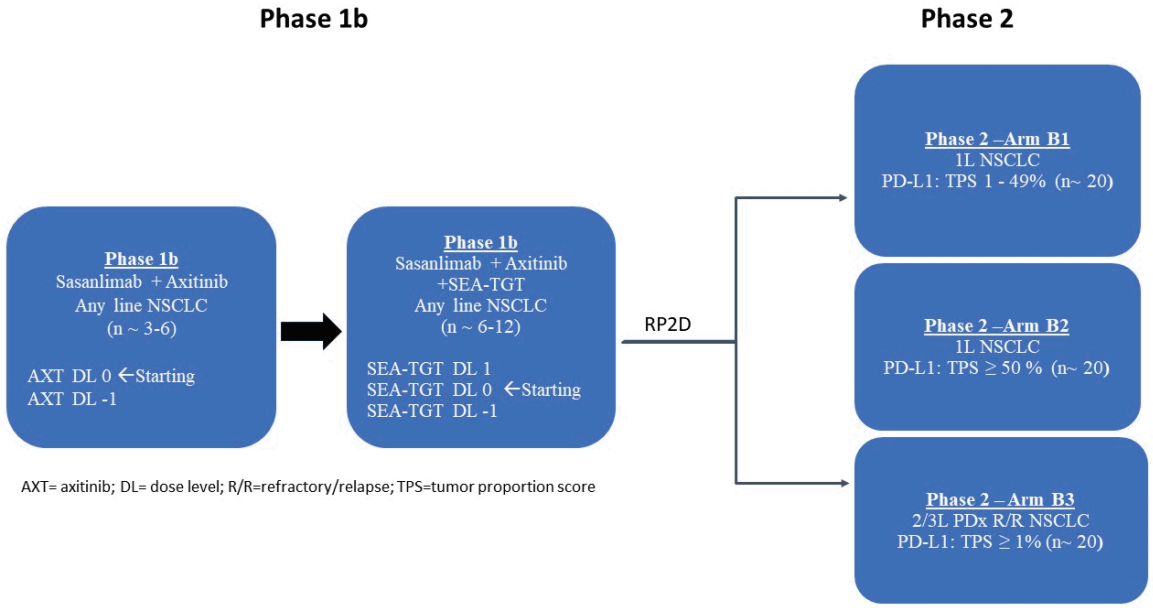
- Population-level summary measure: ORR is defined as the proportion of participants in the analysis population with an OR and 2-sided 95% CI for ORR using the Clopper-Pearson method. Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anti-cancer 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).

13.4. Study Design for Sub-Study B

See Section 4.1 for the overall study design in the master protocol.

Figure 3 illustrates the design of Sub-Study B. Sub-Study B will start with a Phase 1b dose-finding safety part to identify the RP2D for the triplet combination of sasanlimab +axitinib + SEA-TGT. Approximately 20 participants with any line of previous therapy will be enrolled in Phase 1b. Phase 2 will evaluate the anti-tumor activity and additional safety of the triplet combination in approximately 60 participants in the 1L or 2L/3L who have progressed on or after prior PDx treatment. The sasanlimab dose of CCI will remain fixed for all cohorts in Phase 1b and Phase 2 of Sub-Study B. Doses of axitinib and SEA-TGT will be identified via the mTPI dose-finding design. See Sections 13.4.1 and 13.4.2 for more details on the study design of Phase 1b and Phase 2, respectively.

Figure 3. Sub-Study B Design



13.4.1. Phase 1b Design

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 25). The decision to de-escalate (from 5 mg BID to 3 mg BID) will be based on mTPI decision criteria based on the number of DLT evaluable patients 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 allows escalation, then the triplet cohort may be opened. Otherwise, the doublet cohort can be expanded with an additional 3 patients enrolled or de-escalated to the lower dose (3 mg BID) per the mTPI decision criteria.

Table 25. 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 26) 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 patients will be treated at the RP2D of the triplet combination before proceeding to Phase 2.

Table 26. Sub-Study B, Phase 1b, Triplet Cohorts Dose Levels

Dose Level	Sasanlimab	Axitinib*	SEA-TGT
1	CCI	3 or 5 mg BID	3 mg/kg IV Q3W
0 (Starting Dose)	CCI	3 or 5 mg BID	1 mg/kg IV Q3W
-1	CCI	3 or 5 mg BID	0.3 mg/kg 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.

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

Refer to Section 13.9 and Section 13.10.6 for more details on the mTPI design and decision rules.

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.

13.4.2. Phase 2 Design

Once the RP2D of the triplet is defined, the Phase 2 part of the study may be initiated. Patients 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 patients with PD-L1 TPS ≥50% as compared to those with PD-L1 TPS 1-49%.[50] 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 patients who have received prior checkpoint treatment is planned:

- Treatment Arm B3 (n=20): patients 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.

13.4.3. Rationale for the Sub-Study B Combination

See Section 2.1 for the overall study rationale in the master protocol.

Despite advances in the treatment landscape for patients with advanced NSCLC, progression-free survival (PFS) remains modest. While the introduction of PD-1/PD-L1 inhibitors improved clinical outcomes compared to chemotherapy,[49] not all patients benefit from single-agent PD-1/PD-L1 inhibitors.

Recent data for PD-1/PD-L1 inhibitors combined with anti-TIGIT have demonstrated improvement in clinical outcomes over single-agent PD-1/PD-L1 inhibitors in patients with advanced NSCLC, regardless of PD-L1 status:

- CITYSCAPE (NCT03563716), a randomized double-blind, Phase 2 study in advanced NSCLC (N=67; TPS ≥1%) indicated that the addition of anti-TIGIT tiragolumab to atezolizumab resulted in superior ORR & PFS versus atezolizumab + placebo:[50]
    - ORR was 31% vs 16% in the tiragolumab + atezolizumab arm vs placebo + atezolizumab arm. Odds Ratio=2.57 (1.07, 6.14).
    - Median PFS was 5.4 months in the tiragolumab + atezolizumab arm vs 3.6 months in the placebo + atezolizumab arm. HR= 0.57 (0.37, 0.90).
    - A greater magnitude of improvement was seen in the TPS ≥50% group.[50]

- Vibostolimab combined with pembrolizumab in patients with NSCLC whose disease progressed on prior PDx therapy (n=38): ORR was 5% (95% CI: <1, 18) and median duration of response was 13 months (95% CI: 4, 13).[48]
- Vibostolimab combined with pembrolizumab in patients with PDx-naïve NSCLC, (n=41; both TPS ≥1% and <1%): ORR was 29% (95% CI: 16, 46) and median PFS was 5.4 months (95% CI: 2.1, 8.2); median duration of response was not reached.[49]

In addition to inhibition of PD-1/PD-L1 and TIGIT, VEGF pathway inhibition may make the tumor microenvironment more responsive. Successfully targeting these non-overlapping mechanisms may lead to additive or synergistic activity. Single-agent axitinib has

demonstrated antitumor activity in patients with advanced NSCLC who have either received prior therapy or not (see Section 13.2.2.3.1).

The VEGF pathway has been linked with tumor immunosuppression.[51] Elevated expression of genes characteristic of angiogenesis has been associated with reduced OS benefit from avelumab in patients who otherwise show elevated immune activity in tumor.[52] These findings are consistent with the hypothesis that inhibition of the VEGF pathway in conjunction with PD-1/PD-L1 inhibitors will improve patient benefit. This hypothesis has been supported by the clinical studies reported below. Clinical benefit from the combination of avelumab + axitinib in renal cancer and from maintenance avelumab following chemotherapy in advanced urothelial carcinoma is associated with elevated TIGIT expression. TIGIT may therefore limit clinical benefit in the context of anti-tumor immunity enabled by VEGF pathway and PD(L)1 inhibition. The addition of a TIGIT antagonist in such a setting is expected to further improve clinical benefit.

Combinations of PD-1/PD-L1 inhibitors + VEGFR inhibitors (without anti-TIGIT) have demonstrated clinical proof of concept with acceptable safety profiles in several malignancies, including advanced NSCLC:

- Avelumab +axitinib (n=41; PDx naïve advanced NSCLC): ORR=32% (95% CI: 18.1, 48.1). Clinical activity in this population was not associated with PD-L1 expression. Avelumab + axitinib combination responders were associated with an activated immune profile, including the TIGIT pathway.[44]
- Cabozantinib + atezolizumab (n=30; advanced NSCLC patients previously treated with an ICI, 2L setting): ORR of 27% (80% CI: 16, 40).[53]
- Lenvatinib + pembrolizumab: (n=21; 11[52%] received prior ICI, advanced NSCLC): ORR=33% (95% CI: 14.6, 57.0). This combination demonstrated a manageable safety profile and promising antitumor activity in patients with selected solid tumors.[12]

13.4.4. Justification for Dose in Sub-Study B

13.4.4.1. Starting Dose for Phase 1b

The starting dose of sasanlimab in Sub-Study B is CCI and will remain constant throughout the study. Refer to master protocol Section 4.3 for the justification for this starting dose.

The axitinib dose of 5 mg orally twice daily, with or without food, was selected for the starting dose to test dose limiting toxicity in combination with sasanlimab and SEA-TGT. The 5 mg BID dose has proven to be safe and efficacious as a single agent and in combination with checkpoint inhibitors for the treatment of patients with aRCC. It is the dose approved by regulatory authorities worldwide.[43]

The SEA-TGT starting dose was chosen based on PK and PD data in the ongoing first-in-human study SGNTGT-001, in the absence of an MTD. Single-agent doses explored in that study were 0.01, 0.1, 0.3, 1, 3, and 6 mg/kg; SEA-TGT monotherapy demonstrated acceptable safety and tolerability at all dose levels evaluated (Section 13.2.2.3.2). The data

showed strong biologic activity at the lowest dose tested (0.01 mg/kg), sustained target engagement and linear PK were observed starting at 0.3 mg/kg, and minimal PD differences were observed between 1 and 3 mg/kg. Based on these data and the DLT event at 6 mg/kg (Grade 3 pruritic rash), no further dose escalation will occur. Therefore the 1 and 3 mg/kg doses were recommended for further development.

13.4.4.2. Criteria for Dose Escalation/De-Escalation

Refer to Section 13.10.6 for criteria for dose escalation/de-escalation via mTPI for Sub-Study B.

13.4.5. Dose Limiting Toxicity

Refer to master protocol Section 4.3.3 for the definition of DLT.

The DLT observation period is the first 21 days starting with the first dose of any study intervention in the combination.

13.4.6. Maximum Tolerated Dose

The MTD is the highest studied dose level associated with a DLT rate of <35% among the participants treated at that dose level following the mTPI method.

13.4.7. Recommended Phase 2 Dose (RP2D) Definition

Refer to master protocol Section 4.3.5.

13.5. Study Population for Sub-Study B

Participants must meet all of the general inclusion and exclusion criteria as specified in the master protocol (Section 5) plus the following Sub-Study B specific inclusion and exclusion criteria:

13.5.1. Inclusion Criteria for Sub-Study B

Phase 1b and Phase 2:

14. Urinary protein <2+ by urine dipstick. If dipstick is ≥2+, then a 24-hour urinary protein <2g per 24 hours.

15. Baseline blood pressure readings of ≤150 mm Hg (systolic) and ≤90 mm Hg (diastolic), as documented by 2 blood pressure readings taken at least 1 hour apart.

16. Left ventricular ejection fraction (LVEF) ≥ lower limit of normal as assessed by either MUGA scan or ECHO.

Phase 1b only:

17. Any line of therapy for locally advanced/metastatic NSCLC.

Phase 2 only:

18. Able to provide a sufficient amount of plasma and tumor (primary or metastatic, archival or newly obtained); approximately 15 slides (minimum of 10 slides) or block are required for central lab determination of PD-L1 tumor expression and exploratory analyses. If archived tissue is not available and a fresh tumor biopsy is not considered appropriate in the opinion of the investigator, discussion with the sponsor is required.

Phase 2 Arms B1 and B2 (1st Line) only:

19. Previously untreated for advanced/metastatic NSCLC.

20. PD-L1 TPS 1%-49% (Arm B1) or ≥50% (Arm B2), as determined by local lab assay.

Phase 2 Arm B3 (2nd/3rd Line) only:

21. One or 2 prior lines of therapy for advanced/metastatic NSCLC.

    - Must have received prior immune checkpoint inhibitor treatment (at least anti-PD-1/PD-L1 directed therapy) and platinum-based doublet chemotherapy, sequentially or concomitantly, and have documented disease progression while or after receiving the therapy.

22. PD-L1 TPS ≥1% as determined by local laboratory assay.

13.5.2. Exclusion Criteria for Sub-Study B

Phase 1b and Phase 2:

17. Documentation of any tumor-driving molecular alteration including but not limited to: BRAF, activating EGFR (mutations located in exons 18-21), ALK, ROS1, MET, RET. Testing for EGFR mutation is required if status is unknown.

18. Central lung lesion involving major blood vessels.

19. History of Grade ≥ 2 hemoptysis.

20. Gastrointestinal abnormalities including:

    - Inability to take oral medication.
    - Requirement for IV alimentation.
    - Prior surgical procedures affecting absorption, including total gastric resection.
    - Treatment for active peptic ulcer disease in the past 6 months.
    - Active GI bleeding as evidenced by clinically significant hematemesis, hematochezia or melena in the past 3 months without evidence of resolution by endoscopy or colonoscopy.
    - Malabsorption syndromes.

21. Requirement of anticoagulant therapy with oral vitamin K antagonists (see Section 13.6.5.3 for allowed anticoagulant therapies).

22. Active bleeding disorder or other history of significant bleeding episodes within 30 days before first dose of study treatment.

23. History of aneurysm.

24. Evidence of inadequate wound healing.

25. Triplicate average baseline QTcF > 480 msec.

Phase 1b only:

26. Concurrent or anticipated use of strong CYP3A4/5 inducers or strong CYP3A4 inhibitors within 14 days or 5 half-lives (whichever is longer) prior to Cycle 1 Day 1 and throughout the study. The topical use of these drugs is permitted (eg, 2% ketoconazole cream).

Phase 2 only:

27. Prior use of any anti-TIGIT mAb or anti-VEGF pathway therapy.

28. Concurrent or anticipated use of strong CYP3A4/5 inducers within 14 days or 5 half-lives (whichever is longer) prior to Cycle 1 Day 1 and throughout the study.

Phase 2 Arms B1 and B2 (1st- Line) only:

29. Prior treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 agents.

Phase 2 Arm B3 (2nd/3rd - Line) only:

30. Confirmed progressive disease on the first or second imaging tumor assessment after initiation of therapy for advanced/metastatic NSCLC.

13.6. Study Intervention for Sub-Study B

Study Treatments:

For purposes of this sub-study, study intervention refers to sasanlimab, axitinib, and SEA-TGT.

Phase 1b Dose Levels:

See Table 25 and Table 26 for dose scheme in the Doublet Cohorts and Triplet Cohorts, respectively. Participants will receive the following study treatments in each 21-day cycle:

- Sasanlimab SC, CCI (50 mg/mL, 2 mL per vial) on Day 1 of each cycle
- Axitinib:
    - 5 mg BID (1 × 5 mg oral tablet) (Doublet Cohorts Dose Level 0) or
    - 3 mg BID (3 × 1 mg oral tablet) (Doublet Cohorts Dose Level -1)
    - Triplet Cohorts Dose Level will be 1 of the 2 doses above based on dose finding.
    - Intra-patient dose increases up to 10 mg BID will be permitted according to guidelines in Section 13.6.1.1.

- SEA-TGT IV (15 mg/mL, 150 mg/ vial) on Day 1 of each cycle:
  - 1 mg/kg (Triplet Cohorts Dose Level 0) or
  - 3 mg/kg (Triplet Cohorts Dose Level 1) or
  - 0.3 mg/kg (Triplet Cohorts Dose level -1)

Phase 2 Dose Levels:

RP2D of sasanlimab SC CCI + axitinib BID + SEA-TGT IV Q3W

Table 27. Study Interventions: Sub-Study B (Sasanlimab + Axitinib + SEA-TGT)

Intervention Name	Sasanlimab	Axitinib	SEA-TGT
Type	Biologic Product	Small Molecule Product	Biologic Product
Dose Formulation	Solution for injection	Tablet	Solution for IV infusion
Unit Dose Strength	50 mg/mL, 2 mL (100 mg total) vial	1 mg and 5 mg tablets	15 mg/mL (150 mg/vial)
Dosage Level(s)	CCI	3 mg and 5 mg BID	0.3, 1, or 3 mg/kg Q3W
Route of Administration	Subcutaneous	Oral	Intravenous
Use	Experimental	Experimental	Experimental
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.
Former Names or Aliases	PF-06801591 RN888	Inlyta® AG-013736	SGN-TGT

13.6.1. Administration of Sub-Study B Investigational Products

Sasanlimab should be administered first, followed by axitinib, and then SEA-TGT, when possible and in accordance with axitinib BID schedule.

Refer to Section 6.1.1 for details about the administration of sasanlimab, and below for details about administration of the other Sub-Study B products.

13.6.1.1. Administration of Axitinib

Axitinib will be swallowed whole with a glass of water and with or without food. Axitinib should be taken 12 ± 2 hours apart in the morning and in the evening at approximately the

same times every day. If a participant vomits at any time after dosing, the dose should not be re-administered, and the participant should take the next scheduled dose. Any missed dose may be taken up to 3 hours before the next scheduled dose, otherwise it should be skipped. Doses that are omitted for AEs should not be made up during the day, or at the end of the dosing period. Additional information regarding axitinib administration is provided in the IP Manual.

Axitinib will begin on Cycle 1 Day 1 and will be self-administered at home twice per day continuously, except on study visit days, when it should be administered at the study site.

Axitinib intra-patient dose increase is permitted in Phase 1b and Phase 2 after completing 16 weeks of axitinib treatment for participants who tolerate the current axitinib dose with no Grade ≥2 drug-related adverse events for 2 consecutive weeks, and have blood pressure ≤150/90 mm Hg, and are not receiving antihypertensive medication. These participants will have the option to have their axitinib dose increased by one dose level in subsequent cycles, up to a maximum dose of 10 mg BID; the available doses are 3 mg BID, 5 mg BID, 7 mg BID, and 10 mg BID. Particular attention should be provided to a patient's overall safety profile prior to implementing intra-patient dose increase for axitinib.

13.6.1.2. Administration of SEA-TGT

SEA-TGT will be administered on Day 1 of every 21-day cycle by IV infusion. SEA-TGT must not be administered as an IV push or bolus.

Weight-based dosing is based on the participant's actual body weight and weight must be measured at each visit per the SoA. Doses must be adjusted for participants who experience a ≥10% change in weight compared to the body weight used to calculate the initial dose. Other dose adjustments for changes in body weight are permitted per institutional standard. Rounding is permissible within 5% of the nominal dose.

Infusion duration will vary depending on the method of infusion administration and the dose. Refer to the IP Manual for further details. SEA-TGT will be administered via stepwise infusion. In a stepwise infusion, the infusion rate is increased at set time intervals until a defined maximum rate of infusion is reached. As clinical experience with stepwise infusion of SEA-TGT evolves, the maximum rate and/or the infusion rate may change (ie, increase or decrease); the method of administration may also change. The IP Manual will specify any such changes.

Participants will be observed for at least 2 hours post-dose on Cycles 1, 2, and 3.

If a participant does not tolerate the infusion, the infusion duration for that participant may be increased; the infusion duration in subsequent infusions may also be increased per investigator discretion with medical monitor/sponsor approval. Conversely, if a participant tolerates consecutive infusions without IRR Grade >1, the infusion duration may be shortened (ie, administered at a faster rate) at the discretion of the investigator following consultation with the medical monitor/sponsor, the implementation of which may be dose-

cohort specific. For additional information regarding management of IRRs, see Section 13.6.6.1.1.

Pre-medication is not required. However, subjects who experience IRRs may receive subsequent treatment with premedication as indicated in Section 13.10.4. In such cases, premedication should be administered at least 30 minutes prior to the infusion and includes antihistamines (eg, diphenhydramine 50 mg IV or equivalent); famotidine 40 mg IV or equivalent, corticosteroids (e.g., hydrocortisone 100 mg IV or equivalent), or antipyretics, such as acetaminophen/paracetamol (eg, 500 to 1,000 mg oral dose).

Please refer to the IP manual for further instructions on the administration of SEA-TGT.

13.6.2. Preparation, Handling, Storage, Accountability, and Dispensing

Refer to master protocol Section 6.2.

For axitinib, the participant/caregiver should be instructed to maintain the tablets in the bottles provided throughout the course of dosing and return the bottles to the site at the next study visit.

Please refer to the IP manual for further instructions on the preparation and handling of axitinib and SEA-TGT.

13.6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label sub-study that will not be randomized.

13.6.3.1. Allocation to Study Intervention

Refer to master protocol Section 6.3.1.

13.6.4. Study Intervention Compliance

Refer to master protocol Section 6.4.

SEA-TGT must be administered by the appropriately designated study staff at the investigational site and compliance will be documented. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

13.6.5. Concomitant Therapy for Sub-Study B

In addition to concomitant therapy instructions and restrictions in the master protocol Section 6.5, the following concomitant therapy instructions and restrictions apply to Sub-Study B.

13.6.5.1. Permitted Concomitant Therapy Requiring Caution and/or Action

13.6.5.1.1. CYP and UGT Substrates and Inhibitors

Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Concomitant use of strong CYP3A4/5 inhibitors should

be avoided in Phase 1b of Sub-Study B as adjusting the axitinib dose during the DLT period could confound dose selection**.** If concomitant use of a strong CYP3A4/5 inhibitor is unavoidable in Phase 2, consultation with the sponsor is needed prior to concurrent use of the strong CYP3A4/5 inhibitor as the dose of axitinib will need to be adjusted by approximately one-half. Selection of an alternate concomitant medication with no or minimal enzyme inhibition and/or induction potential is recommended in Sub-Study B when co-administered with axitinib.

Participants must avoid consumption of grapefruit, pomegranates, Carambola (starfruit), Seville oranges or products containing the juice of any during the entire study and preferably starting 7 days before the first dose of study interventions, due to potential CYP3A4/5 interaction with axitinib.

For examples of drugs of CYP3A inhibitors to be used with caution or avoided, please see Section 10.13.

13.6.5.2. CYP3A Inducers

Coadministration of axitinib with strong systemic CYP3A4/5 inducers (eg, rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) are prohibited throughout the study (Phase 1 and Phase 2). Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. Moderate CYP3A4/5 inducers (eg, bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible. For examples of moderate and/or strong CYP3A4 inducers, see Section 10.13.

13.6.5.3. Supportive Care

Participants who need to be on anticoagulant therapy during axitinib treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anti-coagulants (including direct Xa inhibitors and direct thrombin inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

13.6.5.4. Surgery

See Section 6.5.7 for master protocol surgery restrictions. If a major surgery or an interventional procedure (eg. endoscopy) is required, treatment with axitinib must be interrupted at least 2 days before the procedure and the patient BP should be monitored closely for hypotension. Patients may resume axitinib 2 weeks after major surgery assuming the wound has completely healed and there are no wound healing complications (eg. delayed healing, wound infection or fistula).

13.6.6. Dose Interruptions and Modifications for Sub-Study B

During the study, any adverse event considered to be related to treatment needs to be further assessed for the potential causality to which of the 3 investigational products. Dose interruption and modification are performed accordingly as explained below.

13.6.6.1. SEA-TGT Dose Modifications

In the event of drug-related toxicity during SEA-TGT therapy, dosing may be delayed and/or reduced as described in Section 13.10.4. SEA-TGT dose delays >21 days should be discussed with the medical monitor. If clinical benefit is demonstrated, subsequent treatment with SEA-TGT may be at a reduced dose level or a prolonged dose interval. The type and severity of the AE observed will be taken into consideration to inform the decision. Participants who experience AEs that meet the criteria for permanent discontinuation of SEA-TGT may not resume SEA-TGT, including at a lower or modified dose.

13.6.6.1.1. Infusion-Related Reactions

IRRs usually occur within 24 hours of infusion and may manifest as a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension. IRRs may occur during the infusion of SEA-TGT. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis. Dose modifications and management of IRRs are in Section 13.10.4.

All supportive measures consistent with optimal participant care should be given throughout the study according to institutional standards. Supportive measures may include, but are not limited to, any or all of the following:

- Slowing, interruption, or other adjustments in the administration of SEA-TGT
- Potential premedication or postmedication for infusions, for example:
  - Antihistamines, such as diphenhydramine 50 mg IV or equivalent
  - Famotidine 40 mg IV or equivalent
  - Antipyretics, such as acetaminophen 500–1,000 mg PO
  - Antiemetics, such as ondansetron
  - IV fluid support, such as normal saline
  - Anti-rigor medication, such as meperidine
  - Vasopressors
  - Corticosteroids, such as hydrocortisone 100 mg IV or equivalent, or methylprednisolone 40 mg IV or equivalent (See Master Section 6.5.6 regarding steroid use in this study)

13.6.6.1.2. Allergic/ Hypersensitivity Reactions

Allergic/hypersensitivity reactions to SEA-TGT are differentiated from IRRs to SEA-TGT by being defined as occurring >24 hours after infusion of SEA-TGT. Allergic/hypersensitivity reactions may manifest in the same manner as IRRs. All participants should be closely observed while receiving SEA-TGT, and after administration in accordance with Section 13.6.1.2. Guidance on SEA-TGT dose modifications is in Section 13.10.4.

See Section 6.6.1 for further information on hypersensitivity reactions.

13.6.6.1.3. Cytokine Release Syndrome

Cytokine release syndrome (CRS) is an acute inflammatory response characterized by fever and may be accompanied by multiple organ dysfunction. ASTCT grading will be used for CRS events, and grading is dependent on the degree of supportive care needed. Grades 1 and 2 have fever with or without constitutional symptoms that require less intensive care. Grade 3 and above require more intensive care, such as vasopressors and high percentage oxygen therapy. Dose modifications and management of CRS are in Section 13.10.4. Monitoring and additional support should be performed per institutional practice.

13.6.6.2. Axitinib Dose Modifications

In the event of drug-related toxicity during axitinib therapy, dosing may be delayed and/or reduced as described in Section 13.10.5. Recommended axitinib dose reductions are provided in Table 28.

The dose of axitinib will also be adjusted for participants with concomitant CYP3A4/5 inhibitor as specified in Section 13.6.5.1.1.

Table 28. Dose Reductions for Axitinib for Toxicity Management

Axitinib Starting Dose	Axitinib First Dose Reduction	Axitinib Second Dose Reduction
3 mg BID	2 mg BID	N/A
5 mg BID	3 mg BID	2 mg BID

NOTE: Dose reduction should be based on the highest AE grade.

13.6.6.2.1. Management of Axitinib-Related Hypertension

Patients should contact the site for guidance if their systolic BP rises above 150 mm Hg, diastolic BP rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated BP (eg, headache, visual disturbance). To treat an increase in BP, standard antihypertensives can be used (eg, thiazide or thiazide-like diuretics, angiotensin II receptor blockers, angiotensin converting-enzyme inhibitors, or dihydropyridine [DHP] calcium channel blockers). Bradycardic agents (eg, beta adrenergic blockers with or without alpha-blocking properties, and non-DHP calcium channel blockers, clonidine, digoxin) should be avoided to the extent possible (See concomitant restrictions in Section 13.6.5).

13.6.6.2.2. Bleeding Risks

The sponsor should be contacted to consider permanent discontinuation of axitinib if a patient develops symptomatic brain metastasis, tumor encasing vasculature, hemoptysis, or other risks for pulmonary hemorrhage while on study treatment. If brain metastases are successfully treated or if participant no longer needs anticoagulation or bleeding disorders resolve, then the treatment could be re-started at the discretion of the investigator and upon discussion with the sponsor.

13.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See Section 7 of the master protocol for discontinuation of study intervention and participant discontinuation/withdrawal.

13.8. Study Assessments and Procedures for Sub-Study B

See Section 8 for master protocol study assessments and procedures, in addition to the following procedures specific to Sub-Study B.

13.8.1. Efficacy Assessments

13.8.1.1. Tumor Response Assessments

Refer to Section 8.1.1 for tumor response assessments.

13.8.2. Safety Assessments

13.8.2.1. Home Blood Pressure Monitoring (Vital Signs)

In addition to the vital signs procedures in the master protocol Section 8.2.2, home BP monitoring will be required. Participants will receive a BP monitoring device and will monitor their BP at home/outside of the clinic at least twice daily (before taking each dose of axitinib) and record the results in the diary. Participants should be instructed to contact the study site immediately for guidance if SBP >150 mm Hg, or DBP >100 mm Hg, or if they develop symptoms perceived to be related to elevated BP (eg, headache, visual disturbance); different BP thresholds may be used per Investigator clinical judgement.

13.8.2.2. Echocardiogram/ Multigated Acquisition Scan (MUGA)

LVEF should be assessed by transthoracic echocardiogram or MUGA and performed as outlined in the SoA.

The same modality used during screening should be used for all subsequent assessments. Additional assessments should also be performed if a participant experiences an AE which may be related to cardiac dysfunction in the opinion of the investigator, or if otherwise clinically indicated.

The details of the echocardiogram/MUGA will not be recorded on a CRF; however, any abnormalities detected on the echocardiogram/MUGA will be reported on the medical history or AE CRF as appropriate.

13.8.3. Treatment of Overdose for Sub-Study B

See master protocol Section 8.4 for sasanlimab overdose information.

13.8.3.1. Treatment of Overdose for Axitinib

There is no specific treatment for axitinib overdose. Supportive measures should be instituted. Please refer to the respective IBs for more information.

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

13.8.3.2. Treatment of Overdose for SEA-TGT

Weight-based dosing for SEA-TGT is based on the participant's actual body weight. An overdose of SEA-TGT is defined as a ≥10% change above the weight-based dose. In the event of an overdose of SEA-TGT, study site personnel should:

- Care for and medically stabilize the participant until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of SEA-TGT.
- Notify the medical monitor/sponsor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of SEA-TGT administered, participant weight) and AEs, if any.

13.8.4. Biomarkers

PD-L1 protein expression in NSCLC is determined by using TPS, which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity, The specimen should be considered to have PD-L1 expression if TPS ≥1% and high PD-L1 expression if TPS ≥50%.

Results of the local laboratory PD-L1 results will be entered in the CRF.

In Phase 2, blood samples or tumor tissue will also be tested centrally to confirm PD-L1 status and for exploratory biomarker analyses. Tumor tissue testing is described in Section 8.8. Tumor tissue collected after the participant was diagnosed with metastatic disease is preferred. The tumor tissue sample must not be from locations that were previously irradiated.

13.9. Statistical Considerations for Sub-Study B

See Section 9 for master protocol statistical considerations and sub-study specifics below.

13.9.1. Estimands and Statistical Hypotheses

13.9.1.1. Estimands

Refer to Section 13.3 for details of estimands.

13.9.1.2. Statistical Consideration for Phase 1b

A safe dose will be determined using the adaptive modified toxicity probability interval (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 rate (pT=0.30).[54] 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.

See Section 13.10.6 for the dose-escalation decisions for the given study that are pre-calculated under the mTPI design and presented in a two-way table.

13.9.1.3. Sample Size Determination

The total sample size is estimated to be approximately 80 participants for the Sub-Study B Phase 1b and Phase 2. The sample size is estimated to be approximately 20 participants for Phase 1b and 60 participants for Phase 2.

13.9.1.3.1. Phase 1b Dose Finding

Approximately 20 participants will be enrolled in the Phase 1b dose finding 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 patients 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 patients 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).

13.9.1.3.2. Phase 2

Phase 2 will enroll approximately 60 subjects who will be dosed at the RP2D of the triplet in 3 treatment arms:

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

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

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

13.9.1.4. Analysis Set

Refer to Section 9.3 for analysis sets.

13.9.1.5. General Considerations

13.9.1.5.1. Primary Endpoints

Phase 1b

The primary endpoint in Phase 1b is DLTs during the DLT-observation period. Refer to Section 9.4.2.

The occurrence of DLTs and AEs constituting DLTs will be summarized for participants in the Phase 1b part as described in Section 13.3.

Phase 2

The primary efficacy endpoint in Phase 2 is OR. Refer to Section 13.3.

ORR will be calculated along with the 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.

13.9.1.5.2. Secondary Endpoints

13.9.1.5.2.1. Efficacy Analyses

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

- DR is defined for participants with confirmed objective response (CR or PR) as the time from the first documentation of OR to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. The censoring rules for DR are as described below for PFS but participants will not be censored in the analysis of DR due to no adequate baseline assessment as only participants with OR are included in the analysis of DR.

- 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. 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 new anti-cancer treatment prior to an event, 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 any adequate post-baseline tumor assessments per RECIST v1.1 will be censored on the date of first dose unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

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

OR will be summarized as the proportion of participants in the analysis population with OR and corresponding 2-sided 95% CI using the Clopper-Pearson method. TTR will be summarized using simple descriptive statistics (eg, median and range). DR, PFS, and OS will be analyzed using Kaplan-Meier methods. Point estimates will be presented with 95% CIs.

13.9.1.5.2.2. Safety Analyses

For Phase 1b primary safety analysis, refer to Section 13.3 for DLT.

For Phase 1b and Phase 2 secondary safety analyses, refer to Sections 9.4.3.2 and 9.4.5.

13.9.1.5.2.3. PK Analyses

Refer to master protocol Section 9.4.3.3 for the analysis of PK endpoints for sasanlimab.

Peak (C_{max}) and trough (C_{trough}) concentrations for axitinib and SEA-TGT will be summarized descriptively (n, mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by cohort/dose and cycle/ day. Exclusions or separate summaries for dose modifications and concomitant medications may be considered in data summaries. Additional analytes may be evaluated as necessary.

Dose-normalized PK parameters (ie, C_{trough}-DN) may be reported as appropriate.

13.9.1.5.2.4. Immunogenicity Analyses

Refer to master protocol Section 9.4.3.4 for the analysis of immunogenicity endpoint for sasanlimab.

For SEA-TGT, the percentage of participants with positive ADA and NAb (if analyzed) will be summarized by treatment and pooled. For participants with positive ADA, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit.

13.9.1.5.2.5. Biomarker Analyses

Refer to master protocol Section 9.4.4.1 for the analysis of biomarker endpoints.

13.9.1.5.3. Exploratory Endpoints

Refer to Section 9.4.4 for biomarker exploratory endpoints.

13.9.1.5.4. Interim Analysis

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

13.10. Supporting Documentation and Operational Considerations for Sub-Study B

13.10.1. Clinical Laboratory Tests for Sub-Study B

In addition to the clinical laboratory tests required in Master Protocol Section 10.2, the tests in Table 29 will be required for participants in Sub-Study B:

Table 29. Clinical Laboratory Tests Added for Sub-Study B

Hematology	Chemistry
• Hematocrit	• Fasting blood glucose • CK • Troponin*

Note: If urinalysis protein is ≥2+ dose adjustment may be needed; See Section 13.10.5.
*Troponin is required only at Screening or C1D1, and whenever clinically indicated throughout the study.

13.10.2. Contraceptive Guidance for Sub-Study B

On the basis of the mechanism of action of sasanlimab and data from approved drugs of the same class, sasanlimab may cause a risk for severe manifestations of developmental toxicity in humans; studies to evaluate the development toxicity of sasanlimab have not been conducted. Therefore, the use of a highly effective method of contraception is required

13.10.2.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 6 months after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s)*:*

- Refrain from donating sperm.

  PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
    - In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 13.10.2.4).

13.10.2.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 13.10.2.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below, during the intervention period and for at least 6 months after the last dose of study intervention, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

13.10.2.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

- Documented hysterectomy;

- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

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

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
    - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
    - Female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

13.10.2.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has

been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
   - Oral;
   - Intravaginal;
   - Transdermal.
2. Progestogen-only hormone contraception associated with inhibition of ovulation:
   - Oral;
   - Injectable.
3. Sexual abstinence:
   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

One of the following acceptable barrier methods must be used in addition to the highly effective methods that are user dependent listed above:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

13.10.3. Examples of Strong and Moderate CYP3A4 Inhibitors

Refer to Section 10.13.

13.10.4. Recommended Dose Modification and Management of SEA-TGT-related Adverse Events

Toxicity	NCI CTCAE Severity Grade	SEA-TGT Dose Modification & AE Management
Hepatotoxicity	ALT and/or AST elevation >3 x ULN and total bilirubin >2 x ULN	Discontinue SEA-TGT.
	ALT and/or AST elevation >3 x ULN with the appearance of clinical symptoms of hepatic injury	Discontinue SEA-TGT.
Other	Grade 3	Withhold SEA-TGT dose until toxicity is Grade ≤ 2 or returns to baseline, and then resume treatment at the same dose level after discussion with the medical monitor/Sponsor.
	Grade 4	Withhold SEA-TGT dose until toxicity is Grade ≤ 2 or returns to baseline. Either resume treatment at a lower dose level after discussion with medical monitor or discontinue study treatment at the discretion of the investigator.
IRR, allergic reaction, or anaphylaxis or CRS*	Grade 1	Monitor vital signs more frequently until symptoms have resolved and subject is medically stable. Administer symptomatic treatment as medically indicated. Consider premedication with subsequent SEA-TGT treatment.
	Grade 2	Hold SEA-TGT treatment. Monitor vital signs more frequently until symptoms have resolved and subject is medically stable. Administer symptomatic treatment as medically indicated. If subject responds promptly and is medically stable in the opinion of the investigator, SEA-TGT treatment may be continued at a slower rate. Consider premedication with subsequent SEA-TGT treatment. Consider slower infusion rate. If recurrent after the above measures, consider dose reduction to 1 dose level below current dose.
	Grade 3	Stop SEA-TGT treatment. Institute additional medical management as indicated.

Toxicity	NCI CTCAE Severity Grade	SEA-TGT Dose Modification & AE Management
		Subjects with an IRR that resolves to baseline or Grade ≤1 within approximately 2 hours after intervention may continue SEA-TGT at a reduced dose for subsequent infusions, if approved by the sponsor/medical monitor. OR Permanently discontinue SEA-TGT.
	Grade 4	Permanently discontinue SEA-TGT.

* ASTCT grading will be used for CRS (CTCAE will be used for all other adverse events)
Note: For detailed irAE management guidelines, refer to Section 10.10.

13.10.5. Recommended Dose Modifications for Axitinib-related Adverse Events

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification
Hematologic Laboratory Abnormalities	Grade 4	Withhold until recovery to Grade ≤ 2. Then, reduce by 1 dose level and resume treatment. Grade 4 lymphopenia not associated with clinical events, eg, opportunistic infection: study treatment may continue without interruption.
AST, ALT with total bilirubin < 2 x ULN and PT/INR < 1.5 x ULN	Grade 2	Withhold until resolution to < 2 x ULN or baseline. Restart at same dose level or one lower dose level.
	Grade 3 and 4	Withhold until resolution to < 2 x ULN or baseline. Restart at one lower dose level.
AST/ALT Elevation with clinically significant hepatic dysfunction (ie, total bilirubin ≥ 2 x ULN excluding biliary obstruction or PT/INR ≥ 1.5 x ULN)		Permanently discontinue axitinib.
Non-hematologic Toxicities, Laboratory Abnormalities and/or Other Drug Related Toxicities	Grade 3	Reduce by 1 dose level. Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry (other than LFTs) laboratory abnormalities may continue at the same dose level per Investigator judgment.
	Grade 4	Other non-hematologic/laboratory and non-laboratory abnormalities: hold treatment until recovery to Grade ≤2 then reduce by 1 dose level and resume treatment. Grade 4 asymptomatic biochemistry laboratory (other than LFTs) abnormality: study treatment may continue without interruption per Investigator's judgment.
Proteinuria	dipstick shows ≥2+	Perform 24-hour urine collection. Dosing may continue while waiting for test results.
	≥ 2 g proteinuria/ 24 hours	Withhold until proteinuria is <2 g/24 hours. Repeat 24-hour urine collection for proteinuria and creatinine clearance (interval at Investigator discretion) until proteinuria is <2 g/24 hours. Then resume at the same dose level or reduce by 1 dose level as per Investigator judgment.

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification
Hypertension	2 systolic BP readings separated by at least 1 hour show systolic pressure >150 mm Hg OR 2 diastolic BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and continue at the same dose level. If on maximal antihypertensive treatment, reduce by 1 dose level. See Section 13.6.6.2 for monitoring/management of axitinib-related hypertension.
	2 systolic BP readings separated by at least 1 hour show systolic pressure >160 mm Hg OR 2 diastolic BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg	Withhold until BP is < 150/100 mm Hg and adjust antihypertensive medication. Then reduce by 1 dose level and resume treatment. If axitinib dosing is temporarily discontinued, participants receiving antihypertensive medications should monitor closely for hypotension. The plasma half-life of axitinib is 2-4 hours and BP usually decreases within 1-2 days following dose interruption. See Section 13.6.6.2 for monitoring/management of axitinib-related hypertension.
	Recurrent hypertension following previous dose reduction (2 systolic BP readings separated by at least 1 hour show systolic pressure >150 mm Hg) OR Recurrent diastolic BP >100 mm Hg (2 BP readings separated by at least 1 hour) following previous dose reduction	Repeat dose reduction by 1 lower dose level. See Section 13.6.6.2 for monitoring/management of axitinib-related hypertension.
Immune-related AE[a]	Grade 2	Hold axitinib until recovery to grade ≤1 and re-start axitinib at the same dose level. Refer to specialist as needed.
	Grade 3-4	Hold axitinib until recovery to grade ≤1 and re-start axitinib at a reduced dose level. Refer to specialist as needed.

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification

a) Axitinib dose modifications for irAEs in this table are for sasanlimab-related irAEs. For detailed irAE management guidelines, refer to Section 10.10.

13.10.6. Detailed Dose Escalation /De-escalation Scheme for mTPI Design for Sasanlimab + Axitinib + SEA-TGT

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[54], 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 30). 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 (ie, minimizes the chance of making a wrong dosing decision).

Table 30. 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):

With 3 participants treated at current dose level

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

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