

Official Protocol Title:	A Phase 1/2 Open-label, Rolling-arm, Umbrella Platform Design of Investigational Agents With or Without Pembrolizumab or Pembrolizumab Alone in Participants with Melanoma (KEYMAKER-U02): Substudy 02A
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Title Page

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Protocol Title: A Phase 1/2 Open-label, Rolling-arm, Umbrella Platform Design of Investigational Agents With or Without Pembrolizumab or Pembrolizumab Alone in Participants with Melanoma (KEYMAKER-U02): Substudy 02A

Protocol Number: 02A-06

Compound Number: MK-3475

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

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Regulatory Agency Identifying Number(s):

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Approval Date: 25 July 2022

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-02A-06	25-JUL-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
3475-02A-05	21-JAN-2022	To clarify enrollment procedures for the rolling arm design of the trial
3475-02A-04	05-JAN-2022	To add one investigational arm: pembrolizumab + ATRA
3475-02A-03	07-JUL-2021	To update the dose modification and toxicity management guidelines for irAEs
3475-02A-02	20-OCT-2020	CCI [REDACTED]
3475-02A-01	23-APR-2020	CCI [REDACTED]
Original Protocol	13-NOV-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Section 10.1.1 Code of Conduct for Clinical Trials	The Code of Conduct for Clinical Trials was updated.	To align with the current Code of Conduct.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/2 Open-label, Rolling-arm, Umbrella Platform Design of Investigational Agents With or Without Pembrolizumab or Pembrolizumab Alone in Participants with Melanoma (KEYMAKER-U02): Substudy 02A

Short Title: Ph 1/2 Substudy of Oncological Treatment(s) in PD-1 Refractory MEL

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Formal hypothesis testing will not be performed in this substudy protocol. The objectives will be evaluated by investigational treatment arm.

Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

In participants with PD-1 refractory melanoma receiving investigational agents with or without pembrolizumab:

Primary Objectives	Primary Endpoints
- To assess the safety and tolerability of investigational treatment combinations based on the proportion of participants with adverse events (AEs).	- Adverse events. - Study intervention discontinuations due to AEs.
- To evaluate objective response rate (ORR) as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).	- Objective Response: Complete response (CR) or partial response (PR).
Secondary Objectives	Secondary Endpoints
- To evaluate the duration of response (DOR) as assessed by BICR per RECIST 1.1.	- DOR: For participants who demonstrate CR or PR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

Overall Design:

Study Phase	Phase 1/Phase 2
Primary Purpose	Treatment
Indication	Melanoma
Population	Male/female participants with melanoma who are at least 18 years of age
Study Type	Interventional
Intervention Model	Parallel This is a multi-site rolling-arm study
Type of Control	No Control arm
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Substudy	The Sponsor estimates that the substudy will require approximately 2.5 years per investigational treatment arm from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last substudy-related contact.

Number of Participants:

This substudy protocol employs a design in which new investigational treatment arms will be open for enrollment on a rolling basis to evaluate investigational treatment combinations with or without pembrolizumab. Therefore, the total number of participants will depend on the number of investigational treatment arms open for enrollment.

A maximum of approximately 100 participants will be enrolled in each investigational treatment arm of this substudy protocol.

Intervention Groups and Duration:

Intervention Groups	<table><tr><th>Sub-study 02A</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Administration</th><th>Regimen/Treatment Period</th><th>Use</th></tr><tr><td></td><td>Pembrolizumab</td><td>200 mg 400 mg</td><td>q3w q6w</td><td>IV</td><td>~2 years</td><td>Experimental</td></tr><tr><td></td><td>Investigational Agent(s)^a</td><td colspan="3">Please see Appendix 6, Section 10.6.1</td><td>~2 years</td><td>Experimental</td></tr></table> q3w=every 3 weeks; q6w=every 6 weeks; IV=intravenously ^a An investigational treatment arm refers to a combination of investigational agent(s) with or without pembrolizumab, or pembrolizumab alone. There can be 1, or more than 1, investigational treatment arm open for enrollment at any given time. The investigational treatment arm(s) open for enrollment are described in Appendix 6, Section 10.6.1.	Sub-study 02A	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use		Pembrolizumab	200 mg 400 mg	q3w q6w	IV	~2 years	Experimental		Investigational Agent(s) ^a	Please see Appendix 6, Section 10.6.1			~2 years	Experimental
Sub-study 02A	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use																
	Pembrolizumab	200 mg 400 mg	q3w q6w	IV	~2 years	Experimental																
	Investigational Agent(s) ^a	Please see Appendix 6, Section 10.6.1			~2 years	Experimental																
Total Number	The total number of investigational treatment arms will depend on the number of investigational agents evaluated. This substudy protocol will include a minimum of 1 investigational treatment arm. Refer to Appendix 6, Section 10.6.1.																					
Duration of Participation	Each participant will participate in this substudy from the time the participant provides documented informed consent through the final protocol-specified contact. After a Screening Phase of up to 28 days, each participant will receive study intervention for approximately 2 years or until disease progression is radiographically documented per RECIST 1.1 by the investigator, unacceptable AEs, withdrawal of consent or death, intercurrent illness that prevents further administration of study intervention, investigator’s decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of study intervention, whichever occurs first. Participants who attain an investigator-determined confirmed complete response (CR) may consider stopping study intervention after at least 24 weeks of study intervention has been administered. In addition, if a confirmed CR per RECIST 1.1 is attained, at least 2 additional doses of study intervention must be received after CR is first documented. Participants will be permitted to continue study intervention beyond RECIST 1.1-defined disease progression as long as the treating investigator considers that the participant may experience clinical benefit with continued intervention, and the participant is tolerating study intervention as per iRECIST (RECIST 1.1 for immune-based therapeutics). Treatment beyond disease progression per iRECIST may be permitted upon Sponsor consultation and approval. After the End of Treatment (EOT), each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy.																					

	Participants who discontinue due to radiographic disease progression will move into posttreatment Safety and Survival Follow-up. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment Safety and Follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 by the investigator, a nonstudy cancer treatment is initiated, consent is withdrawn, pregnancy, death, or becoming lost to follow-up. All participants will be followed for overall survival (OS) until death, withdrawal of consent, or the end of this substudy. Please see Appendix 6, Section 10.6.2 for additional details. Once the substudy objectives are achieved or the substudy has ended, participants will be discontinued from this substudy protocol and may be enrolled in an extension study to continue assessments and treatment, if available.
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Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Substudy governance considerations are outlined in Appendix 1. For a description of the internal DMC, see Section 10.1.4.2.	

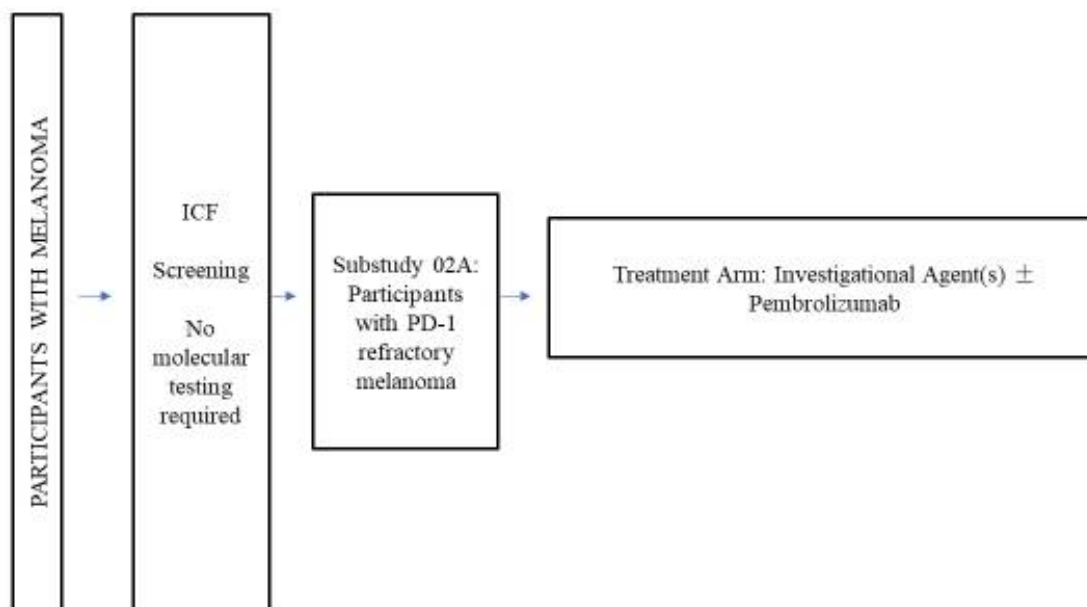
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 12.

1.2 Schema

The overall substudy design is depicted in [Figure 1](#).

Figure 1 Substudy 02A Design Overview



1.3 Schedule of Activities

Refer to Appendix 6, Section 10.6.2.1 for the SoA for each investigational treatment arm.

2 INTRODUCTION

2.1 Study Rationale

Despite clear advances that have been taking place in the treatment of early as well as advanced melanoma in recent years, there are still medical needs and opportunities to improve the overall outcome of melanoma patients. This substudy protocol provides the framework for evaluating investigational agents (added to the backbone of a PD-1 receptor inhibitor or without an anti-PD-1 backbone) in patients who might benefit from these drugs and who are in need of new treatment options. The infrastructure of this substudy protocol enables the rolling assignment of investigational agents as they become available in an efficient and cost-effective manner. This substudy protocol will include patients with PD-1 refractory melanoma. The rationale for this substudy protocol is described in Section 2.2.2.

2.1.1 Rationale for Use of Standard-of-Care Pembrolizumab

Not applicable for this substudy protocol.

2.1.2 Rationale for Choice Investigational Agents

Investigational agents that successfully attain a RP2D in Phase 1 studies, and whose mechanisms of action and toxicity profile make them logical candidates for subsequent study in Phase 1/2 in oncology will be tested in this substudy protocol. The candidate investigational agents are currently being evaluated in early phase studies as monotherapy alone and in combination with pembrolizumab.

See Appendix 6, Section 10.6.2.3 for a detailed rationale for each investigational agent.

2.2 Background

2.2.1 Melanoma Epidemiology and Current Therapeutic Options

Melanoma is the most serious form of skin cancer and affects adults of all ages. The 5-year prevalence of melanoma in the EU is approximately 326,000 patients with an incidence of approximately 83,000 new cases per year and approximately 16,000 deaths annually [WHO Health Organization 2012]. Melanoma accounts for approximately 5% of all new cases of cancer in the US. The incidence of melanoma continues to increase by almost 3% per year in the US. This translates to approximately 76,000 new cases a year with approximately 9000 associated deaths. The male-to-female incidence ratio of melanoma is 1.4:1 [Siegel, R., et al 2012]. The 5-year survival rate before the use of anti-PD-1 agents was 17% once patients had Stage IV disease [American Cancer Society 2016].

High-dose interleukin-2 was the first treatment to modify the natural history of patients with metastatic melanoma and may be curative for a small fraction of patients. However, its severe toxicity limited its application to carefully selected patients treated at centers with experience in managing the side effects of treatment. More recent research led to the development of immunotherapy using checkpoint inhibitors such as anti-PD-1 antibodies (pembrolizumab and nivolumab), and the anti-CTLA-4 antibody (ipilimumab and tremelimumab) and targeted therapy such as the BRAF and/or MEK inhibition (dabrafenib and/or trametinib, respectively). Both approaches prolong PFS and OS compared with chemotherapy [UpToDate, Inc. 2015], thus, they are standard therapeutic options for patients with melanoma. More recently, the combination of a BRAF inhibitor plus a MEK inhibitor showed increased efficacy and a better safety profile compared with BRAF inhibition alone as 1L therapy in patients with advanced melanoma. Both the combination of dabrafenib and trametinib or vemurafenib and cobimetinib are approved as 1L therapy in BRAF V600E mutation-positive melanoma patients [Robert, C., et al 2015] [Larkin, J., et al 2014]. The KEYNOTE-006 Phase 3 study showed superior efficacy of pembrolizumab compared with ipilimumab in PFS and OS [Eggermont, A. M. M., et al 2018]. Similarly, nivolumab was studied in patients with previously untreated advanced melanoma compared with dacarbazine, and nivolumab showed superior efficacy compared with dacarbazine among previously untreated patients who had metastatic melanoma without BRAF mutation [Robert, C., et al 2015].

In 2014, the FDA approved both nivolumab and pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression after ipilimumab and, if BRAF V600E mutation-positive, a BRAF inhibitor. The European Commission also approved pembrolizumab and nivolumab, for both 1L and previously treated patients with advanced melanoma.

Combination immunotherapy (anti-PD-1 + anti-CTLA-4) has shown high ORRs in patients with metastatic melanoma (ORR 58%); however, half of patients experienced significant toxicity from the treatment regimen [Valsecchi, M. E. 2015] [Postow, M. A., et al 2015] and survival benefit for this approach compared with anti-PD-1 agents has yet to be shown.

There have also been recent advances in the treatment of earlier melanoma tumor settings, such as high-risk Stage III patients after complete surgical resection of the primary tumor. Both PD-1 inhibitors pembrolizumab and nivolumab and the combination of BRAF and MEK inhibitors administered in the adjuvant setting have led to a decrease in the risk of recurrence compared with their respective controls [Eggermont, A. M. M., et al 2018] [Weber, J., et al 2017] [Long, G. V., et al 2017]. The combination of BRAF and MEK inhibitors has also shown an increase in OS compared with placebo in the COMBI-AD study (ie, Dabrafenib With Trametinib in the Adjuvant Treatment of High-risk BRAF V600 Mutation-positive Melanoma).

With all of this significant advancement in the treatment of both adjuvant and advanced melanoma, which has led to a change in the treatment paradigm of melanoma patients, new medical needs have emerged as well as opportunities to continue to improve the outcomes of these patients.

2.2.2 Melanoma Medical Needs

2.2.2.1 PD-1 Refractory Melanoma

Analyses of clinical study data have identified 2 broad patterns of resistance to PD-1 inhibitors in patients with advanced melanoma: patients who fail to respond to PD-1 inhibitors administered as 1L therapy (also known as innate resistance), and patients who initially respond to therapy but eventually develop disease progression (also known as acquired resistance) [Pitt, J. M., et al 2016] [Restifo, N. P., et al 2016] [O'Donnell, J. S., et al 2017] [Sharma, P., et al 2017].

In addition, with the approval of anti-PD-1 agents in Stage III melanoma, while the majority of patients treated with adjuvant pembrolizumab are recurrence-free at 1 year (pembrolizumab 1-year RFS is 75.4% [95% CI: 71.3 to 78.9]), some patients do not benefit from adjuvant therapy and experience disease recurrence while on anti-PD-1 therapy or shortly thereafter [Eggermont, A. M. M., et al 2018] [Weber, J., et al 2017] [Long, G. V., et al 2017].

Several mechanisms have been proposed to explain resistance to PD-1 inhibition such as insufficient antitumor T-cell generation, inadequate antitumor T-cell effector function, or impaired T-cell memory. However, these mechanisms remain largely unknown [Jenkins, R. W., et al 2018].

Clinical data in this setting is very limited and unsatisfactory. Retrospective data in melanoma patients previously exposed to anti-PD-1 inhibitors showed an ORR to available checkpoint inhibitors (CTLA-4 and CTLA-4 + PD-1 combination) of 16% and 21%, respectively [Zimmer, L., et al 2017].

Phase 2 data of pembrolizumab plus ipilimumab immediately after progression on anti-PD-1 therapy in 17 evaluable melanoma patients showed an ORR of 47% and a disease control rate of 76% [Olsonm, D., et al 2018]. Recent results from the Phase 2 ILLUMINATE-204 study investigating tilisotolimod, an intratumorally delivered toll-like receptor agonist in combination with ipilimumab (Yervoy®) in 15 patients with unresectable or metastatic melanoma after failure of PD-1 inhibitor treatment, showed an ORR of 22.4% and a disease control rate of 71.4% [Haymaker, C., et al 2020].

Therefore, this population represents a high medical need and effective therapies are urgently needed.

2.2.2.2 First-line (1L) Advanced Melanoma

Unresectable Stage III or Stage IV melanoma has historically been resistant to anticancer therapies and was associated with a median OS of less than 1 year. However, with the arrival of new therapies including targeted therapies such as BRAF and/or MEK inhibition for BRAF-mutant melanoma and immune-checkpoint-based immunotherapy (anti-CTLA-4 and anti-PD-1 inhibitors), OS for patients with metastatic melanoma has tripled [Robert, C., et al 2015] [Robert, C., et al 2015] [Robert, C., et al 2015].

Mature data from KEYNOTE-006, with a median follow-up of 57.7 months (range: 0.03 to 62.1 months) confirms the long-term benefit of pembrolizumab in patients with advanced melanoma. The 5-year OS rate for patients treated with pembrolizumab was 38.7% and the 4-year PFS rate was 23.0% [Robert, C., et al 2019].

Despite these results, there is a large population of advanced melanoma patients (approximately 60% of all unresectable Stage III or Stage IV melanoma patients who receive anti-PD-1 inhibitors as 1L therapy for their advanced disease) who do not respond to therapy with anti-PD-1 agents.

Thus, the goal of evaluating combination strategies in this setting is to improve the overall outcome of patients with 1L advanced melanoma.

2.2.2.3 Neoadjuvant Melanoma

Surgery is the main treatment for Stage I or Stage II melanoma (tumor limited to the primary site) and Stage III melanoma (tumor invading regional lymph nodes). Although the long-term RFS rates for most patients with low-risk Stage I and Stage II melanoma are excellent after surgery, patients who have high-risk features such as tumor-involved lymph nodes (Stage III) have poorer outcomes, with an average 5-year OS of approximately 50% [Gershenwald, J. E., et al 2017]. As mentioned above, adjuvant therapy with PD-1 inhibitors pembrolizumab and nivolumab and the combination of BRAF and MEK inhibitors is standard of care in patients with high-risk Stage III melanoma with lymph node involvement after complete resection.

While adequate and effective surgery is the goal of early treatment of primary melanoma, some cases with bulky nodal involvement are at high risk of local and distant recurrence despite upfront surgical resection. Neoadjuvant treatment offers the benefit of an early on-treatment pathological specimen that can be profiled for additional biomarkers and correlated with survival (pathological response as a surrogate marker for RFS and OS). Neoadjuvant treatment also allows to determine the efficacy of a treatment-of-interest within an individual patient and reduce the tumor burden before surgery, facilitating the procedure. Recent preclinical data also provide support for the superior activity of T-cell checkpoint blockade when given before surgery [Liu, J., et al 2016].

Patients with bulky resectable disease have been treated in pilot studies using a neoadjuvant approach with targeted therapy, and more recently, checkpoint inhibitors.

A Phase 2 clinical study of melanoma patients receiving neoadjuvant plus adjuvant dabrafenib and trametinib showed a RECIST 1.1 response rate after neoadjuvant-targeted therapy of 85% (11 of 13 participants) and a pCR rate of 58% (7 of 12 participants). Compared with patients randomized to surgery followed by adjuvant targeted therapy, there was a statistically significant difference in the 12-month EFS favoring the neoadjuvant arm [Amaria, R. N., et al 2018].

Another Phase 2 clinical study in 20 participants with palpable Stage III melanoma randomized participants to receive ipilimumab 3 mg/kg and nivolumab 1 mg/kg, as either

4 doses after surgery (adjuvant arm) or 2 doses before surgery and 2 doses after surgery (neoadjuvant arm). Neoadjuvant therapy was feasible, with all participants undergoing surgery at the preplanned time point. However, in both arms, 9 of 10 participants experienced 1 or more Grade 3 or Grade 4 AEs. Pathological responses were achieved in 7 of 9 participants (78%) treated in the neoadjuvant arm, and 3 of 9 participants (33%) had pCRs. None of these participants have relapsed with a median follow-up of 25.6 months [Blank, C. U., et al 2018].

Results from a separate randomized Phase 2 study of 2 doses of neoadjuvant nivolumab 3 mg/kg versus 2 doses of combined ipilimumab 3 mg/kg with nivolumab 1 mg/kg in 23 patients with high-risk resectable melanoma yielded high response rates (RECIST 1.1 ORR 73% [8 of 11 participants], pCR 45% [5 of 11 participants]) with substantial toxicity (73% Grade 3 treatment-related AEs) for the combination, whereas treatment with nivolumab monotherapy yielded modest responses (ORR 25% [3 of 12 participants], pCR 25% [3 of 12 participants]) and lower toxicity (8% Grade 3 treatment-related AEs) [Amaria, R. N., et al 2018].

Data with 1 dose of neoadjuvant pembrolizumab 200-mg fixed dose in 27 participants with resectable Stage III and Stage IV melanoma followed by curative resection and pembrolizumab therapy for 1 year confirmed that all participants were able to undergo surgery with no perioperative complications and the safety profile was consistent with the overall safety profile of pembrolizumab. Complete or near complete pathologic response was seen in 30% (n = 8) of participants at the time of resection and 1-year RFS was 55% [MedPage Today, LLC 2019].

The neoadjuvant clinical data described above is based on a small number of treated patients. However, because of the high risk of recurrence in Stage III melanoma with bulky resectable disease, the changing role of lymph node surgery in Stage III disease [Faries, M. B., et al 2017] and the advantages of neoadjuvant approaches described above, including an early prognostic readout, there is a high need to identify active combinations in this setting with an acceptable risk-benefit profile.

2.3 Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ T cells/FoxP3+ Tregs correlates with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune

responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable-type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta, protein kinase C theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to but distinct from that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in melanoma.

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Preclinical in vitro data show that pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Refer to the IB/approved labeling for detailed background information on pembrolizumab.

2.4 Investigational Agent Pharmaceutical and Therapeutic Background

Please refer to Appendix 6, Section 10.6.2.2 for background information on the investigational agents that are currently being assessed in this substudy protocol.

2.5 Scientific Rationale for the Combination of Investigational Agents With or Without Pembrolizumab

Please refer to Appendix 6, Section 10.6.2.3 for information on the scientific rationale for the combination of investigational agents with or without pembrolizumab that are currently being assessed in this substudy protocol.

2.6 Clinical Data on the Combination of Investigational Agents With or Without Pembrolizumab

Please refer to Appendix 6, Section 10.6.2.4 for information on the clinical data on the combination of investigational agents with or without pembrolizumab that are currently being assessed in this substudy protocol.

2.7 Benefit/Risk Assessment

Beneficial effects of pembrolizumab have been seen in several melanoma studies to date. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in single-arm and randomized studies as monotherapy (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-054).

Given the relevance of improving and expanding treatment options for patients with melanoma, there is a high need for novel combinations in different tumor settings, as described in Section 2.2.2.

However, participants in clinical studies cannot be guaranteed of direct benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.



Additional details regarding specific benefits and risks for participants participating in this clinical substudy may be found in the accompanying IB and ICF documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Formal hypothesis testing will not be performed in this substudy protocol. The objectives will be evaluated by investigational treatment arm.

Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

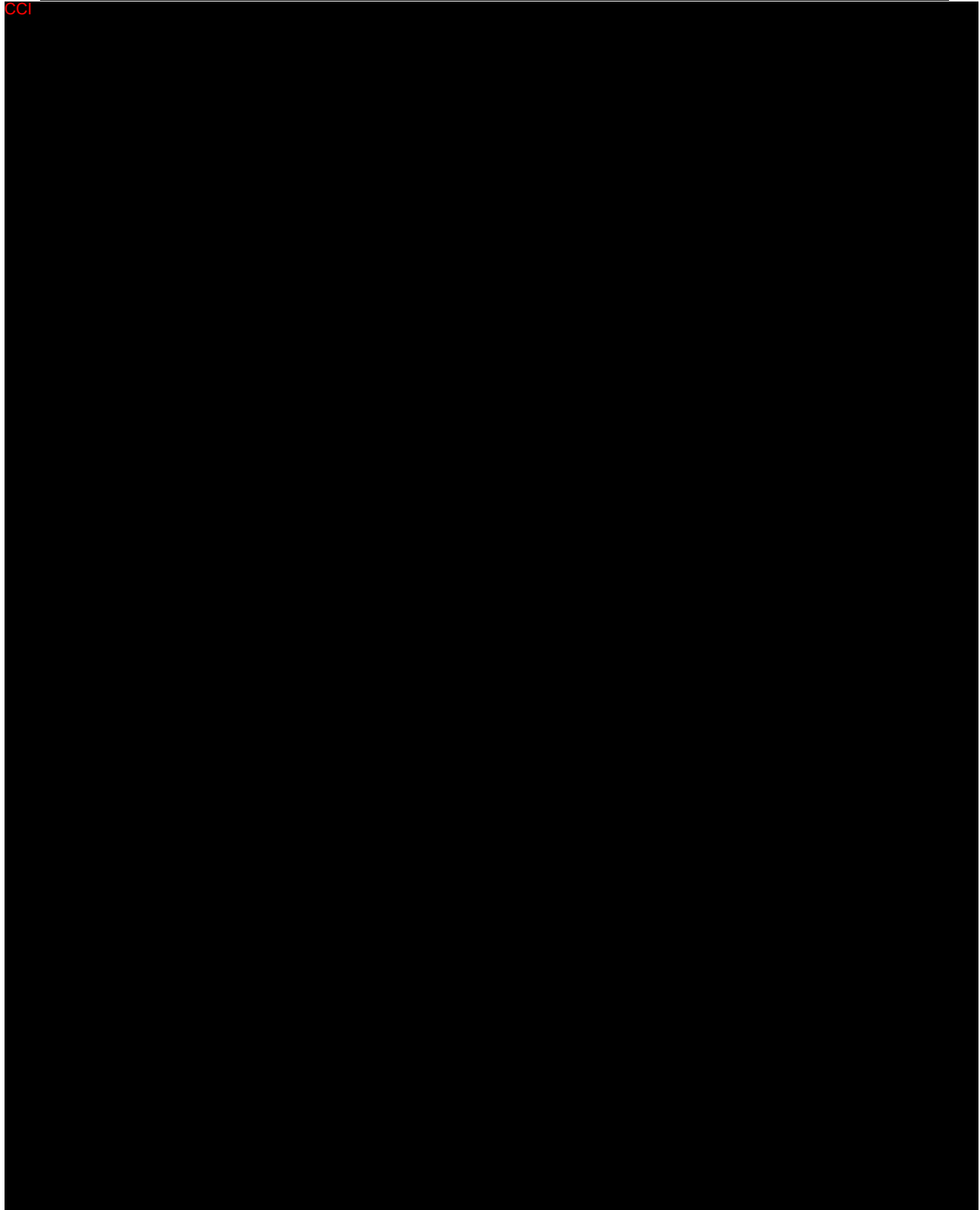
In participants with PD-1 refractory melanoma receiving investigational agents with or without pembrolizumab:

Objectives	Endpoints
Primary	
To assess the safety and tolerability of investigational treatment combinations based on the proportion of participants with adverse events (AEs).	- Adverse events. - Study intervention discontinuations due to AEs.
To evaluate objective response rate (ORR) as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).	Objective Response: Complete response (CR) or partial response (PR).
Secondary	
To evaluate the duration of response (DOR) as assessed by BICR per RECIST 1.1.	DOR: For participants who show CR or PR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
Tertiary/Exploratory	

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Objectives	Endpoints
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4 STUDY DESIGN

4.1 Overall Design of the Substudy

The Master Protocol is a Phase 1/2, rolling-arm, multicenter, open-label, CCI design study that will evaluate within this substudy protocol the efficacy of investigational agents with or without pembrolizumab for the treatment of PD-1 refractory melanoma. Preliminary efficacy from this substudy protocol will be evaluated by using ORR per RECIST 1.1, as determined by BICR. Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

In this substudy protocol, an investigational treatment arm refers to a unique investigational agent or a combination of investigational agents with or without pembrolizumab. Investigational agents will only be added to this substudy protocol after an initial evaluation of safety and tolerability when administered alone and in combination with pembrolizumab has been completed and a RP2D has been identified. Pembrolizumab-based/non-pembrolizumab-based combinations of agents without an identified RP2D will need to complete a Safety Lead-in Phase within this substudy protocol.

Specific procedures to be performed during this substudy, as well as their prescribed times and associated visit windows, are outlined in the SoA in Appendix 6, Section 10.6.2.1. Details of each procedure are provided in Section 8 and in Appendix 6, Section 10.6.2.17, Section 10.6.2.18, Section 10.6.2.19, Section 10.6.2.20, Section 10.6.2.21, and Section 10.6.2.22.

4.1.1 Investigational Treatment Arms

Please refer to Appendix 6, Section 10.6.2.5.1 for information on the investigational treatment arms that are currently being assessed in this substudy protocol.

This substudy protocol will include participants with PD-1 refractory melanoma. PD-1 refractory melanoma must have progressed on treatment with an anti-PD-1/L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. Participants must have received at least 2 doses of an approved anti-PD-1/L1 mAb and have shown disease progression after PD-1/L1 as defined by RECIST 1.1. Additional criteria are described in Section 5.1. No approved therapies exist in this setting and therefore, this population is considered as having a high need. This substudy protocol will consist of 1 or more investigational treatment arms evaluating pembrolizumab-based/non-pembrolizumab-based combinations. If more than 1 investigational treatment arm is open at any given time, participants will be randomly assigned to 1 of the investigational treatment arms open for enrollment.

This substudy protocol will only consist of an Efficacy Phase once the RP2D of a combination has been established in a separate Phase 1 study. However, when the RP2D of the combination has not previously been established (ie, pembrolizumab combined with 2 or more investigational agents), this substudy protocol will have 2 phases: an initial Safety

Lead-in Phase, in which the preliminary RP2D of the combination will be established, followed by an Efficacy Phase.

During this substudy protocol, an internal DMC will monitor all safety information to ensure participant safety in accordance with a separate charter. The internal DMC will serve as the primary reviewer of treatment-level safety results and will make recommendations for discontinuation of each substudy intervention based on safety considerations. The internal DMC is composed of members of Sponsor staff, none of whom are directly associated with the conduct of this substudy. The internal DMC responsibilities and review schedules will be outlined in the internal DMC charter. There are up to 2 planned IAs.

Endpoints are described in Section 4.2.1.

4.1.1.1 Safety Lead-in Phase (Only for Combinations Without an Established RP2D)

The RP2D for each investigational agent, alone or in combination with pembrolizumab, was established in a separate, prior Phase 1 study and will be used as the starting dose for the Safety Lead-in Phase in this study. ^{CCI}

^{CCI} An event will be considered a DLT if it occurs during a prespecified time period (as defined in Appendix 6, Section 10.6.2.5.1) from the first dose of study intervention and meets at least 1 of the criteria described in Section 6.6.5. Initially, 3 DLT evaluable participants will be enrolled at the starting dose (refer to Section 4.3).

Participants will be evaluated for DLTs for 1 cycle from first dose of study intervention before further enrollment. Participants may be replaced if they meet the criteria described in Section 5.5. If the initial dose level is too toxic, newly enrolled participants may be treated at a lower dose level. Dose recommendations for the next participants will depend on the observed number of DLTs in the first 3 DLT evaluable participants and the mTPI table (Table 5). ^{CCI}

4.1.1.2 Efficacy Phase ^{CCI}

After the RP2D is established in the Safety Lead-in Phase, additional participants will be enrolled at the corresponding RP2D in the respective investigational treatment arm(s) for the efficacy evaluation.

The Efficacy Phase will enroll up to 40 base participants and an additional 60 expansion
CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.1.1.3 All Substudy Participants

A maximum of approximately 100 participants are targeted for enrollment per investigational treatment arm, with a minimum enrollment of 10 participants possible.

Participants will continue study intervention for approximately 2 years or until disease progression is radiographically documented per RECIST 1.1 by the investigator, unacceptable AEs, or any other discontinuation criterion has been met (Section 7.1). Participants who discontinue study intervention due to radiographic disease progression will move into posttreatment Safety and Survival Follow-up (Section 8.12.5 and Section 8.12.6).

Participants who discontinue study intervention for reasons other than radiographic disease progression will have posttreatment safety assessments and follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 by the investigator, a nonstudy cancer treatment is initiated, consent is withdrawn, pregnancy, death, or becoming lost to follow-up. All participants will be followed for OS until death, withdrawal of consent, or the end of this substudy (Section 8.12.6).

An investigational treatment arm will be discontinued if the totality of the data does not support a favorable risk-benefit profile (see Section 4.1.5).

Follow-up visits and imaging schedules will be scheduled per the SoA (Appendix 6, Section 10.6.2.1). The primary safety endpoints of this substudy protocol are the proportion of participants with AEs and the proportion of participants who discontinue study intervention due to AEs; the primary efficacy endpoint is the ORR by BICR per RECIST 1.1.

Safety evaluations will include AE monitoring, physical examinations, clinical laboratory parameters (hematology and chemistry), vital signs, and assessment of ECOG performance status (see Appendix 10). Adverse events will be monitored throughout this substudy and graded in severity according to the guidelines outlined in the NCI CTCAE version 5.0. This substudy will be conducted in conformance with Good Clinical Practices.

4.1.2 Stratification

No stratification factors will be used in this substudy protocol.

4.1.3 Randomization/Allocation

Participants in this substudy protocol will be randomly allocated across all open treatment arms (Figure 1). If only 1 investigational treatment arm available for enrollment, the treatment assignment will be deterministic.

4.1.3.1 Rationale for Randomization

Even though there is no intent to compare the treatment effect across investigational treatment arms, CCI [REDACTED]

Randomization to investigational treatment arms will occur centrally using an IRT system. More details on randomization are provided in Section 6.3.1.

4.1.4 Criteria for Adding Arms

The Sponsor will decide if an investigational agent should be studied in this substudy protocol based on the mechanism of action and toxicity profile observed in the Phase 1 studies. Once an investigational agent has been chosen, the Sponsor will decide in which investigational treatment arm(s) the investigational agent will be open for enrollment. The decision for which investigational treatment arm(s) a specific investigational agent will be assigned will be proposed by each study team based on the mechanism of action and the clinical development landscape.

New investigational agents will be added to this substudy protocol through an amendment by adding a new section in Appendix 6, specific to that investigational agent (eg, Appendix 6, Section 10.6.2). In addition, [Table 11](#) will be revised accordingly.

4.1.5 Criteria for Removing Arms

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The totality of the data across all substudies, including the safety profile, ORR, and change in tumor size from baseline will be included in the evaluation of either dropping or continuing an investigational treatment arm at an IA. Additionally, enrollment into an arm may stop early for issues related to enrollment or if risk/benefit is deemed unacceptable for a given investigational combination.

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However, the decision to further study the investigational agent(s) will be based on the totality of data from all substudies in the umbrella platform study, the data from other studies for the same investigational agent, as well as other factors such as the landscape for melanoma treatment at the time.

Investigational agents terminated for randomization/allocation will be inactivated from each substudy through an amendment. In addition, [Table 11](#) and [Table 12](#) will be revised accordingly.

4.2 Scientific Rationale for Substudy Design

The goal of this substudy protocol is to evaluate, on a rolling basis, the efficacy of investigational treatment arms in participants with PD-1 refractory melanoma to identify the investigational agent(s) that, when used in combination, are superior to the current treatment options/historical control available.

The umbrella platform study design provides the framework for testing investigational agents in this substudy protocol of patients with PD-1 refractory melanoma who might benefit from adding these drugs to the backbone of a PD-1 receptor blockade or from testing investigational agents without a PD-1 backbone. The infrastructure of this study enables the rolling assignment of investigational agents that are entering this Phase 1/2 study in an efficient and cost-effective manner to study the impact of each investigational treatment arm for these patients in need.

This is the only substudy protocol with a Safety Lead-in Phase, since this is the only substudy that might evaluate combinations without an established RP2D.

The study employs an adaptive design in which treatments are added and/or inactivated from the study on an ongoing basis. Refer to Section 4.1.4 and Section 4.1.5, respectively.

4.2.1 Rationale for Endpoints

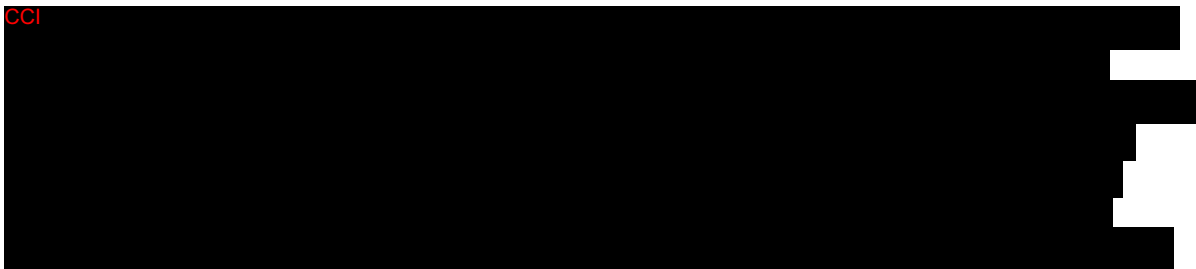
4.2.1.1 Efficacy Endpoints

The primary efficacy objective of this substudy protocol is to evaluate the antitumor effect of various investigational agents with or without pembrolizumab in participants with PD-1 refractory melanoma.

This substudy protocol will use objective response as the primary efficacy endpoint. Objective response rate is defined as the proportion of participants who have best response as CR or PR. Responses are based on BICR using RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). Objective response rate is an appropriate endpoint to evaluate the antitumor activity of investigational treatment arms.

A treatment effect measured by ORR can support accelerated approval, support traditional approval, or represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, number of CRs, durability of response, disease setting, location of the tumors, available therapy, and risk-benefit relationship.

This substudy protocol will use DOR as a secondary efficacy endpoint. Duration of response is defined as the time from the earliest date of qualifying response until the earliest date of disease progression or death from any cause, whichever comes first. Duration of response per RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, assessed by BICR will serve as an additional measure of efficacy and is a commonly accepted endpoint by both regulatory authorities and the oncology community.



CCI [REDACTED]

[REDACTED]

iRECIST will also be used by the local site to make treatment decisions once disease progression has been documented per RECIST 1.1 by investigator.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility. Eligibility will also be prospectively assessed by BICR based on RECIST 1.1.

4.2.1.1.2 RECIST 1.1 for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen after treatment with pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor 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 participants treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not fully capture the treatment benefits from immunotherapeutic agents such as pembrolizumab. An analysis of participants with melanoma enrolled in KEYNOTE-001 showed that 7% of evaluable participants experienced delayed or early tumor pseudoprogression. Of note, participants who had progressive disease by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer OS than participants with progressive disease by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 10% of participants. These findings support the need to apply a modification to RECIST 1.1 that considers the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

iRECIST assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US FDA and the EMA [Seymour, L., et al 2017]. The unidimensional measurement of

target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression per iRECIST which may be used by investigators to assess tumor progression and make treatment decisions.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. Adverse events will be assessed as defined by the NCI CTCAE, version 5.0.

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities. As part of the analyses for this substudy, participants will provide information regarding their HRQoL via the following assessment tools: EORTC QLQ-C30 and EQ-5D-5L questionnaire. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health status/QoL scale (items 29 and 30). The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies.

The endpoint of TTD with deterioration defined as a 10-points or more decrease from baseline is widely viewed as being clinically significant when interpreting the results of randomized clinical studies that use the EORTC QLQ-C30.

4.2.1.3.2 EQ-5D-5L

The EQ-5D-5L questionnaire is a standardized instrument for use as a measure of health outcome. The EQ-5D-5L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life years. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates their general state of health at the time of the assessment. The EQ-5D-5L will always be completed by participants after completing the EORTC QLQ-C30. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability.

4.2.1.4

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4.2.1.5

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4.3 Justification for Dose

4.3.1 Rationale for Pembrolizumab Dosing Plan

The planned doses of pembrolizumab for this substudy protocol are 200 mg q3w and 400 mg q6w.

Rationale for 200 mg q3w dosing:

The totality of data generated in the KEYTRUDA® development program indicate that 200 mg q3w is one of the appropriate dosing options of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies showing flat dose- and exposure-efficacy relationships from 2 mg/kg q3w to 10 mg/kg q2w,
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg q3w across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg q3w.

Among the 8 randomized, dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg q3w versus 10 mg/kg q3w (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg q3w versus 10 mg/kg q2w (KN001 Cohort B3, KN001 Cohort F2, and

KN006). All of these studies showed flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure.

The 2 mg/kg (or 200 mg fixed dose) q3w provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin lymphoma, confirming 200 mg q3w as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg q3w. First, PK data in KN001 evaluating target-mediated drug disposition conclusively showed saturation of PD-1 in systemic circulation at doses much lower than 200 mg q3w. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg q3w achieves full PD-1 saturation in both blood and tumor. Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg q3w fixed dose and 2 mg/kg q3w dose. Supported by these PK characteristics and given that fixed dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg q3w fixed dose was selected for evaluation across all pembrolizumab protocols.

Rationale for 400 mg q6w dosing:

A 400 mg q6w dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg q3w in all treatment settings in which 200 mg q3w pembrolizumab is currently approved. Specifically, the dosing regimen of 400 mg q6w for pembrolizumab is considered adequate based on M&S analyses, given the following rationale:

Pharmacokinetic simulations showing that in terms of pembrolizumab exposures:

- C_{avg} (or AUC) at 400 mg q6w is similar to that at the approved 200 mg q3w dose, thus bridging efficacy between dosing regimens.
- C_{min} at 400 mg q6w are generally within the range of those achieved with 2 mg/kg or 200 mg q3w in the majority (>99%) of patients.
- C_{max} at 400 mg q6w are well below the C_{max} for the highest clinically tested dose of 10 mg/kg q2w, supporting that the safety profile for 400 mg q6w should be comparable to the established safety profile of pembrolizumab.
- E-R for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg q6w is expected to be similar to that at 200 mg or 2 mg/kg q3w, given the similar exposures; thus 400 mg q6w is expected to be efficacious across indications.

- The EMA has adopted a positive opinion recommending the approval of a new extended dosing schedule for KEYTRUDA® for all approved monotherapy indications in the EU. The CHMP opinion supports a new recommended dose of 400 mg q6w delivered intravenously over 30 minutes. The 400 mg q6w dosing schedule would provide patients in the EU with 2 approved dosing options of pembrolizumab [Merck & Co., Inc. 2019].

4.3.2 Rationale for Investigational Agent Dosing Plan

Please refer to Appendix 6, Section 10.6.2.6.1 for the rationale for dosing information for the investigational agents that are currently being assessed in this substudy protocol.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Ample notification will be provided in the event of Sponsor decision to no longer supply the investigational agent or pembrolizumab.

5 STUDY POPULATION

Male and female participants with melanoma who are at least 18 years of age will be enrolled in this substudy protocol.

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

Refer to Appendix 6, Section 10.6.2.7 and Section 10.6.2.8 for additional inclusion or exclusion criteria, respectively, specific to the investigational agent(s) before randomization/allocation to ensure the participant meets all eligibility criteria.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the substudy if the participant:

Type of Participant and Disease Characteristics

1. Has histologically or cytologically confirmed melanoma.
2. Has unresectable Stage III or Stage IV melanoma, per AJCC 8th Edition Staging Criteria (see Appendix 9), not amenable to local therapy.
3. Has the presence of at least 1 measurable lesion by CT or MRI per RECIST 1.1 as confirmed by BICR.
 - a. Cutaneous lesions and other superficial lesions are not considered measurable lesions but may be considered as nontarget lesions.
 - b. If participants have only 1 measurable lesion per RECIST 1.1, the biopsy specimen should be obtained from the nontarget lesion or archival tissue. If biopsy specimen was obtained from a lone target lesion, a repeat screening CT must be obtained post biopsy and measurable disease confirmed by BICR.
 - c. Lesions that are in an area that has been previously irradiated should not be considered measurable unless there has been documented growth of the lesions since the completion of radiation.
4. Has progressed on treatment with an anti-PD-1/L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:
 - a. Received at least 2 doses of an approved anti-PD-1/L1 mAb.
 - b. Showed disease progression after PD-1/L1 as defined by RECIST 1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid clinical progression. This determination is made by the investigator. Once progressive disease is confirmed per iRECIST by the investigator, the initial date of progressive disease documentation will be considered the date of disease progression.
 - c. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb.
 - d. Participants who receive anti-PD-1 therapy as adjuvant treatment after complete resection of Stage III or IV melanoma and have disease recurrence (unresectable loco-regional disease or distant metastases) while on active treatment or within 6 months of stopping anti-PD-1. For these participants, the following applies: 1) a second assessment to confirm disease progression beyond recurrence is not

required; and 2) they must have received at least 2 prior doses of anti-PD-1/L1 mAb. This participant population may be limited to approximately 20% in each investigational treatment arm.

- e. Prior therapy with CTLA-4 inhibitors will be allowed.
 - f. Participants with BRAF V600E/K mutant melanoma must have received prior therapy with a BRAF/MEK inhibitor combination (either in the adjuvant or metastatic treatment setting).
5. The site's study team must have reviewed imaging to determine that radiographic progression has occurred per RECIST 1.1 in the setting of participants exhibiting rapid progression or for participants who progressed on adjuvant therapy with an anti-PD-1/L1 agent. All other participants must have imaging documenting progression per RECIST 1.1 and iRECIST after initiation of an anti-PD-1/L1 agent (see Section 8.2.1.1 for further details).
6. Has not received more than 3 lines of therapy for their advanced melanoma.
7. Has provided a tumor biopsy.
- a. Participants must submit tumor sample during Screening for adequacy of tumor tissue at a central pathology laboratory. Participants who do not submit a tumor tissue sample will not be randomized/allocated. Confirmation of adequacy of tumor tissue is not required before randomization/allocation.
 - b. Newly obtained tissue is preferred and must be collected after progression on prior anti-PD-1/L1 agent. In cases where newly obtained tissue is not possible to provide, an archival sample obtained after progression on a PD-1/L1 agent shall be accepted upon Sponsor approval.
- Note: This condition may be waived if collecting a tumor biopsy post PD-L1 progression is not feasible, or not in the best interest of the participant, after Sponsor approval.
- c. If a fresh tissue sample is submitted, it is preferred that the tumor biopsy is not obtained from a lone target lesion. If the biopsy specimen was obtained from a lone target lesion, a repeat screening CT must be obtained post biopsy and measurable disease confirmed by BICR.

Demographics

- 8. Is male or female from 18 years to 120 years at the time of providing informed consent.
- 9. Has an ECOG performance status 0 to 1 (as assessed within 7 days of the first dose of study intervention, see Appendix 10).

Male Participants

10. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Contraception measures for the investigational agents are specified in Appendix 6, Section 10.6.2.7.

Male participants are eligible to participate if they agree to the following during treatment with the investigational agents.

- Be abstinent from heterosexual intercourse 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 unless confirmed to be azoospermic (vasectomized or secondary to medical cause)
- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse.

Female Participants

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

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

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for the time specified in Appendix 6, Section 10.6.2.7 after the last dose of study intervention. Refer to Appendix 6, Section 10.6.1 for specific investigational agents. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.
- 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.

Note: For female participants, contraception measures for the investigational agents are specified in Appendix 5 and Appendix 6, Section 10.6.2.7.

Informed Consent

12. The participant (or legally acceptable representative if applicable) has provided documented informed consent/assent for the study.

Additional Categories

13. Has adequate organ function as detailed in [Table 1](#). Specimens must be collected within 7 days before the first dose of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1500/\mu\text{L}$
Platelets	$\geq 100\,000/\mu\text{L}$
Hemoglobin	$\geq 9.0\text{ g/dL}$ or $\geq 5.6\text{ mmol/L}^a$
Renal	
Creatinine <u>OR</u> Measured or calculated ^b creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times \text{ULN}$ <u>OR</u> $\geq 30\text{ mL/min}$ for participant with creatinine levels $> 1.5 \times \text{institutional ULN}$
Hepatic	
Total bilirubin	$\leq 1.5 \times \text{ULN}$ <u>OR</u> direct bilirubin $\leq \text{ULN}$ for participants with total bilirubin levels $> 1.5 \times \text{ULN}$ except for unconjugated hyperbilirubinemia of Gilbert's syndrome
AST (SGOT) and ALT (SGPT), and ALP	$\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ for participants with liver metastases) ^c
Coagulation	
International normalized ratio (INR) <u>OR</u> prothrombin time (PT) Activated partial thromboplastin time (aPTT)/PTT	$\leq 1.5 \times \text{ULN}$ unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
ALP=alkaline phosphatase; ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; GFR=glomerular filtration rate; ULN=upper limit of normal. a. Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. b. Creatinine clearance (CrCl) should be calculated per institutional standard. c. Participants with ALP values > 3 times the ULN and known to have bone metastases can be included. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

14. Has resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia). If the participant received major surgery or radiation therapy of $> 30\text{ Gy}$, they must have recovered from the toxicity (resolved to $\leq$ Grade 1) and/or complications from the intervention. Note: Grade 2 hypothyroidism will be allowed.

5.2 Exclusion Criteria

The participant must be excluded from the substudy if the participant:

Medical Conditions

1. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study intervention. Participants with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
2. Has a known additional malignancy that is progressing or requires active treatment within the past 2 years. Exceptions to the secondary malignancy exclusion include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new non-ulcerated primary melanoma <1 mm in depth with no nodal involvement, Grade 1 follicular lymphoma or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy.
3. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated CNS metastases may participate provided they are stable (without evidence of progression by imaging before the first dose of study intervention as evidenced by 2 scans at least 4 weeks apart providing stability, and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases confirmed by repeat imaging, and have not required steroids for at least 14 days before study intervention. The second scan showing stability may be used as baseline scan if acquired within the Screening Phase.
Note: Participants with asymptomatic previously untreated brain metastases may participate provided there are ≤ 3 total lesions in the brain and their longest diameter is <1 cm. Stability of these lesions does not need to be confirmed by repeat imaging.

Baseline MRI brain scan will be obtained for all participants. Brain CT scan should only be used when MRI is contraindicated. The second brain MRI showing stability may be used as baseline scan if acquired within the Screening Phase.
4. Has ocular or mucosal melanoma.
5. Has known hypersensitivity to active substances or any of their excipients including previous clinically significant hypersensitivity reaction to treatment with another mAb. For a list of excipients, refer to the respective IB.
6. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

7. Has an active infection requiring systemic therapy.
8. Has known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies). No testing of HIV is required unless mandated by local health authority (See Appendix 11 for country-specific requirements).
9. Has known history of hepatitis B (defined as HBsAg reactive) or known hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
Note: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority (See Appendix 11 for country-specific requirements).
10. Has a history of (noninfectious) pneumonitis that required steroids or current pneumonitis.
11. Has a history of active tuberculosis (TB; *Bacillus tuberculosis*). (See Appendix 11 for country-specific requirements).
12. A WOCBP who has a positive urine pregnancy test within 24 hours before randomization or treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
Note: If more than 24 hours have elapsed between the Screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for the participant to start receiving study intervention.

Prior/Concomitant Therapy

13. Has received prior systemic anticancer therapy including investigational agents within 4 weeks before randomization/allocation.

Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy and/or ≤Grade 2 endocrinopathy may be eligible.

Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention before starting study intervention.
14. Has received prior radiotherapy within 2 weeks of first dose of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
15. Has had major surgery (<3 weeks before first dose of study intervention)
Note: If the participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention before first dose of study intervention. Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

16. Has received a live vaccine within 30 days before the first dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

17. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.
Note: Participants who have entered the Follow-up Phase of an investigational study may participate if it has been 4 weeks since the last dose of the previous investigational agent.

Diagnostic Assessments

None.

Other Exclusions

18. Has a history or has current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the substudy, interfere with the participation for the full duration of the substudy, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
19. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the substudy, starting with the Screening visit through 120 days after the last dose of study intervention.
20. Has had an allogeneic tissue/solid organ transplant.

5.3 Lifestyle Considerations

None for pembrolizumab. Please refer to Appendix 6, Section 10.6.2.9 for lifestyle considerations for specific investigational agents.

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting. Please refer to Appendix 6, Section 10.6.2.9 for investigational-agent-specific meals and dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

None for pembrolizumab. Please refer to Appendix 6, Section 10.6.2.9 for caffeine, alcohol, and tobacco considerations for specific investigational agents.

5.3.3 Activity Restrictions

None for pembrolizumab. Please refer to Appendix 6, Section 10.6.2.9 for activity restrictions for specific investigational agents.

5.3.4 Investigational Agent Contraception, Pregnancy, and Use in Nursing Women

Study intervention may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study intervention may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during this substudy. To participate in this substudy, participants of childbearing potential must adhere to the contraception requirements (Appendix 5) from the day of study intervention initiation (or 14 days before the initiation of study intervention for oral contraception) throughout this substudy period up to 120 days after the last dose of study intervention. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into this substudy.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are subsequently not randomized in this substudy. 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 AEs or SAEs meeting reporting requirements as outlined in the entry guidelines.

5.5 Participant Replacement Strategy

To determine safety in the Safety Lead-in Phase, all participants selected must meet the criteria for evaluability during the DLT window (see also Appendix 6, Section 10.6.2.5.1). Participants are considered non-evaluable for DLT assessment and will be replaced if:

- They are enrolled but not treated
- They discontinue from the substudy before completing all the safety evaluations during the DLT window for reasons other than treatment-related AEs (eg, disease progression)
- They discontinue from the substudy before completing the DLT window and do not experience a DLT before discontinuation
- They receive <75% of the total investigational agent infusion (eg, because the infusion has to be discontinued due to an infusion reaction) or <60% of the planned doses of an oral agent during the DLT window and do not experience a DLT.

DLT non-evaluable participants will not be included in the DLT evaluation in the Safety Lead-in Phase.

If a participant experiences a DLT in the Safety Lead-in Phase, the investigator and Sponsor will discuss the case. If the investigator feels the participant is deriving clinical benefit from the study intervention and is deemed clinically stable, the participant may be allowed to continue if agreed to by the Sponsor. Otherwise, the participant should discontinue study intervention. Participants must meet the following criteria for clinical stability:

- Participants must have adequate organ function as indicated by the laboratory values,
- Participants must have no evidence of disease progression, and
- Participants must have an ECOG performance status of 0 or 1.

6 STUDY INTERVENTION

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

Clinical supplies will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this substudy protocol are outlined in [Table 2](#). See also Appendix 6, Section 10.6.2.10 for specific details on particular investigational agents to be used in this substudy protocol.

Table 2 Study Interventions

Intervention Group	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strengths	Dosage Levels	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Substudy 02A	Experimental	Pembrolizumab	Drug	Solution for Infusion	25 mg/mL	200 mg 400 mg	IV Infusion	q3w q6w	Experimental	IMP	Central
Substudy 02A	Experimental	Investigational Agent ^a	Drug	Solution for Infusion	TBD	TBD	IV Infusion	TBD	Experimental	IMP	Central
Substudy 02A	Experimental	Investigational Agent ^a	Drug	Capsule	TBD	TBD	Oral	TBD	Experimental	IMP	Central

IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product; q3w=every 3 weeks, q6w=every 6 weeks; TBD=to be determined.

Note: Definition of IMP and NIMP is based on guidance issued by the European Commission. Regional and/or country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

a Refer to Appendix 6, Section 10.6.2.10 for specific dosing information on the investigational agent(s).

All study interventions will be administered on an outpatient basis. Pembrolizumab, as indicated in Table 2, will be provided centrally by the Sponsor. Investigational agents indicated in Appendix 6 Table 13 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab and the investigational agents are provided in the Pharmacy Manual.

Refer to Appendix 6, Section 10.6.2.11.1 for a description of dose preparation and handling, storage, and accountability of the investigational agents.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the substudy 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) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

No control arm (standard-of-care pembrolizumab monotherapy) will be used in this substudy protocol. When there is more than 1 investigational treatment arm open for enrollment, randomization will be utilized to minimize bias. Randomization to investigational treatment arms will occur centrally using an IRT system.

6.3.2 Stratification

No stratification factors will be used in this substudy protocol.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the study intervention administered.

6.4 Study Intervention Compliance

Study intervention(s) will be administered by the investigator and/or study staff. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol-specified treatment ≥ 12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. When applicable, study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

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

See Appendix 6, Section 10.6.2.13 for investigational agent-specific compliance information.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment period. If a clinical indication for any medication or vaccination is specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication (including over-the-counter medications) or therapy administered to the participant during this substudy (starting at the date of informed consent) will be recorded on the appropriate CRF. The investigator will record the AE for which the concomitant medication/therapy was administered on the appropriate CRF. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into this substudy, the investigator will record the medical condition on the appropriate CRF.

All prior medications (including over-the-counter medications) administered within 28 days before the first dose of study intervention and any concomitant therapy administered to the participant during the study (starting at the date of informed consent) and up to 30 days after the last dose of study intervention should be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the participant's health, and that is not expected to interfere with the evaluation of or interact with the study intervention, may be continued during this substudy.

6.5.1 Allowed Concomitant Medications

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs) may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study intervention. Antiemetic or any other prophylaxis should be considered in accordance with institutional guidelines.

Any additional procedural or participant-specific particularities should be discussed with the investigator and the Sponsor.

6.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening, Treatment Phase, and Posttreatment Safety Follow-up Visit of this substudy protocol:

- Concurrent anticancer therapies such as chemotherapy, targeted therapies, antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy not specified in this protocol.

Note: Topical anticancer agents to treat skin lesions (eg, in situ melanoma or squamous cell carcinoma) are allowed, excluding skin metastasis of melanoma.

- Palliative surgery to treat a nontarget symptomatic solitary lesion or to the brain will be allowed after documented progressive disease. Palliative surgery to treat nontarget lesions without documentation of progressive disease will need Sponsor consultation and approval. Palliative surgery of target lesions without documentation of progressive disease is not allowed.
- Palliative radiotherapy to treat a nontarget symptomatic solitary lesion(s) or to the brain, will be allowed after documented progressive disease. Palliative radiotherapy to treat nontarget lesions without documentation of progressive disease will need Sponsor consultation and approval. Palliative radiotherapy of target lesions without documentation of progressive disease is not allowed.
- Other concurrent investigational drugs not specified in this protocol.
- Live vaccines within 30 days and while participating in this substudy. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist[®]) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have immunologic etiology. Physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone equivalent may be used during this substudy. Note: Inhaled steroids are allowed for management of asthma or seasonal allergies.

For participants who, in an assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of study intervention, and further participation in the substudy must be discussed and agreed upon with the Sponsor. If participants receive additional anticancer therapies, this will be judged to represent evidence of disease progression, and study intervention will be discontinued. These participants should complete all EOT assessments and continue to be followed for survival in the Follow-up Period.

After the Posttreatment Safety Follow-up Visit there are no prohibited therapies.

6.5.3 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology for immunotherapeutic agents and other etiologies for investigational agents with a different mechanism of action are outlined along with the dose modification guidelines in each substudy. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive

care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or investigational agent(s) being explored in this protocol.

Note: If after the evaluation of an event, it is determined to be not related to pembrolizumab or any other investigational agents, the investigator does not need to follow the treatment guidance.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of an event.

6.5.4 Hematopoietic Growth Factors

Primary prophylactic use of G-CSF may be used per the discretion of the treating physician and in line with local guidelines.

6.5.5 Drug Interactions

Refer to Appendix 6, Section 10.6.2.14.3 for a description of drug interactions of the investigational agents.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Modification for Pembrolizumab

Pembrolizumab dose reductions are not permitted. Pembrolizumab intervention may be interrupted or discontinued due to toxicity. Pembrolizumab may be interrupted for a maximum of 12 weeks. An interruption of pembrolizumab for more than 12 weeks will require Sponsor approval before intervention can be resumed (see Section 6.4).

6.6.1.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in [Table 3](#).

Note: For Arm 3, if pembrolizumab is discontinued, ATRA must also be discontinued.

Please see Appendix 6, Section 10.6.2.15 for additional details, and Appendix 11 for country-specific requirements.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last treatment. 3. The corticosteroid taper should begin when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to $\leq$ Grade 1 after corticosteroid taper.				
irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	- Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper - Add prophylactic antibiotics for opportunistic infections	- Monitor participants for signs and symptoms of pneumonitis - Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	- Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) - Participants with $\geq$ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis - Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 ^a	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 ^b or 4 ^c	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold ^d	- Initiate insulin replacement therapy for participants with T1DM - Administer antihyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue ^d		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue ^d		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event ^e		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

^a AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

^b AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

^c AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

^d The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

^e Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.6.1.2 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reactions are provided in [Table 4](#).

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 hours ($\pm$ 30 minutes) prior to infusion of pembrolizumab with: - Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). - Acetaminophen 500-1000 mg orally (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: - Epinephrine** - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal antiinflammatory drugs; PO = by mouth. Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov		

6.6.1.3 Other Allowed Dose Interruptions for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study intervention. Participants should be placed back on study intervention within 3 weeks of the scheduled interruption for pembrolizumab, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's substudy record. Imaging should not be delayed for delays in cycle treatment.

6.6.2 Dose Modification for Investigational Agent Intervention

Please refer to Appendix 6, Section 10.6.2.15.1 for dose modification information on the investigational agents that are currently being assessed in this substudy protocol.

6.6.2.1 Other Allowed Dose Interruptions

Please refer to Appendix 6, Section 10.6.2.15.1.1 for other allowed dose interruption information on the investigational agents that are currently being assessed in this substudy protocol.

6.6.3 Dose Modifications for Overlapping Toxicities

For overlapping toxicities where it is unclear if the event is related to pembrolizumab or the investigational agent(s), it is recommended to hold all study intervention and initiate management as outlined in Section 6.6.1 and Appendix 6, Section 10.6.2.15. If toxicity does not improve, the investigator should consider discontinuing the participant.

6.6.4 Modified Toxicity Probability Interval in the Safety Lead-In Phase

CCI [REDACTED]

[REDACTED]

CCI



CCI [REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

6.6.5 Definition of Dose-limiting Toxicity

Dose-limiting toxicities will be defined from toxicities observed during the first cycle of treatment (see also Appendix 6, Section 10.6.2.5.1). The occurrence of any of the following toxicities will be considered a DLT unless the investigator assessment determines the toxicity to be clearly not related to the study intervention:

- Any Grade 4 nonhematologic toxicity (not laboratory)
- Any Grade 4 hematologic toxicity lasting >7 days, except:
 - Grade 4 platelet count decreased of any duration
 - Grade 3 platelet count decreased if associated with bleeding
 - Grade 4 lymphopenia lasting ≥ 21 days
- Any nonhematologic AE $\geq$ Grade 3, with the following exceptions:
 - Grade 3 fatigue lasting ≤ 7 days
 - Grade 3 diarrhea, nausea, vomiting without use of antiemetics or antidiarrheals per standard of care
 - Grade 3 rash, if not adequately treated with steroids
 - ATRA-related headache not optimally managed with supportive care therapies (acetaminophen or nonsteroidal anti-inflammatory medication) or that does not resolve within 72 hours of stopping ATRA. A participant's choice to stop all ATRA, due to headache alone will not be considered a dose-limiting toxicity
- Any Grade 3 nonhematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care
- Any clinically significant Grade 3 or Grade 4 nonhematologic laboratory abnormality, if:
 - medical intervention is required to treat the participant,
 - the abnormality leads to hospitalization,
 - the abnormality persists for >1 week, OR
 - the abnormality results in a DILI (refer to Section 8.4.7 for criteria).

Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.

- Any febrile neutropenia Grade 3 or Grade 4
- Any treatment-related AE that causes the participant to discontinue study intervention during the DLT window
- Any Grade 5 toxicity
- Any treatment-related toxicity that causes a >2-week delay in initiation of Cycle 3

6.7 Intervention After the End of the Study

No study-specified intervention after the end of this substudy protocol is planned.

6.8 Clinical Supplies Disclosure

This substudy is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are aware of the specific treatment assignments. Study intervention is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

6.9.1 Study Site Retention Samples

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the substudy.

As certain data on clinical events beyond study intervention discontinuation may be important to the substudy, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will continue to participate in the substudy as specified in the SoA and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the substudy plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from substudy intervention but continue to be monitored in the substudy for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Documented disease progression.

Note: Participants will be permitted to continue treatment beyond documented RECIST 1.1-defined progression if investigator-assessed clinical stability is observed, and the participant is tolerating study intervention (Section 8). Treatment beyond progressive disease per iRECIST may be permitted in this substudy protocol after Sponsor consultation and approval. A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017].

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy, which requires active treatment. Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new non-ulcerated primary melanoma <1 mm in depth with no nodal involvement, Grade 1 follicular lymphoma or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy. Exceptions should be discussed with the Sponsor before continuing therapy.
- Recurrent Grade 2 pneumonitis and other AEs that may require treatment discontinuation per Section 6.6 (Dose Modification).
- Completion of approximately 2 years of study intervention.

For participants who are discontinued from study intervention but continue to be monitored in the substudy, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from substudy intervention is "permanent." Once a participant is discontinued from study intervention, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

Specific details regarding procedures to be performed at the time of withdrawal from the substudy, are outlined in Section 8.1.9. The procedures to be performed should a participant

repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required substudy visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- CCI [REDACTED]

8 STUDY ASSESSMENTS AND PROCEDURES

- Substudy procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for substudy conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All substudy-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing

may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical substudy. If there are changes to the participant's status during the substudy (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place (See Appendix 11 for country-specific requirements.).

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the substudy.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the substudy. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the substudy and the study population are to be included in the study informed consent form.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

Not applicable.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for this substudy protocol.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research substudy. The card will contain substudy site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization/allocation, site personnel will add the treatment/randomization number to the participant identification card.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this substudy protocol will be recorded separately and not listed as medical history.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting this substudy protocol. Treatment for the disease for which the participant has enrolled in this substudy protocol will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during this substudy.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.

All new anticancer therapy initiated after this substudy protocol start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study intervention(s), the study intervention(s) should be discontinued, and the participant will

move into the Survival Follow-up Phase; if a participant initiates a new anticancer therapy within 30 days after the last dose of study intervention, the 30-day Safety Follow-up Visit should occur before the first dose of the new therapy.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization/allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization/allocation. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number within this substudy.

8.1.8 Study Intervention Administration

Study intervention will be administered by the investigator and/or substudy staff.

8.1.8.1 Timing of Dose Administration

Study intervention will be administered on Day 1 of every treatment cycle. Study intervention should begin within 24 hours of randomization. See SoA for timing of administration of investigational agents.

8.1.8.1.1 Pembrolizumab Administration

Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of every treatment cycle if given q3w or on Day 1 of every other treatment cycle if given q6w. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/ +10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

8.1.8.1.2 Investigational Agents Administration

See Appendix 6, Section 10.6.2.17.1.1 and the Pharmacy Manual for specific details on the timing and administration procedures for each investigational agent. Investigational agents will be administered after pembrolizumab.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining substudy visits.

When a participant withdraws from participation in this substudy protocol, all applicable activities scheduled for the final substudy visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label substudy; there is no blinding for this substudy protocol.

8.1.11 Domiciling

Participants will not be domiciled.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

Immunogenicity assessments will not be performed for pembrolizumab. Refer to Appendix 6, Section 10.6.2.18 for required immunogenicity assessments for specific investigational agents.

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the CIV can be found in the SIM. Diagnostic quality CT of the chest, abdomen, pelvis, and neck (if disease present) is required at baseline and at all scheduled follow-up visits. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of stand-alone CT if it is of diagnostic quality per the Site Imaging Manual. If a site's standard practice is to follow participants with PET/CT rather than a dedicated CT, these initial images must show progression on prior anti-PD-1/L1 inhibitor, consistent with RECIST 1.1 and iRECIST per Section 5.1. There will be no allowance for "worsening of existing disease" by PET if there is NO new lesion. There must be a NEW lesion seen either on PET/CT, or diagnostic quality CT. Refer to the Site Imaging Manual for additional information.

For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Magnetic resonance imaging

is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout this substudy to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Brain imaging is required for all participants at Screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

All scheduled images performed at Screening for all substudy participants from the sites will be submitted to the CIV to verify the presence of measurable disease by BICR per RECIST 1.1 before randomization. All subsequent scheduled images for all substudy participants from the sites will be submitted to the CIV. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, and captures radiologic progression based on investigator assessment, should also be submitted to the CIV.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days before the date of the first dose of study intervention. If additional time is needed for initial image submission (screening imaging for real-time confirmation of measurable disease per RECIST 1.1 by BICR) and CIV diagnostic quality review an extension of the screening window of up to 7 days may be approved after mandatory Sponsor consultation. Tumor imaging performed as part of routine clinical management is acceptable for use as Screening tumor imaging if it is of diagnostic quality and performed within 28 days before the first dose of study intervention. All imaging visits have a scheduling window of ± 7 days.

Participants in this substudy with previously treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging (confirmed by MRI if MRI was used at prior imaging or confirmed by CT imaging if CT used at prior imaging before the first dose of study intervention as evidenced by 2 scans at least 4 weeks apart providing stability). In addition, participants with previously untreated brain metastases may also participate provided they meet the inclusion and exclusion described in Section 5. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases and have not used steroids for brain metastases for at least 14 days before substudy initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

Digital photographs documenting measurable cutaneous lesions should be obtained if the cutaneous lesion is included as part of the nontarget lesions for disease assessment according to RECIST 1.1. Copies of the photograph should be forwarded to the central imaging vendor for potential retrospective analysis. The timing for capturing cutaneous lesion photographs should follow the same schedule as the imaging scans. The requirements for the digital

photographs and the process for transmitting photographs to the central imaging vendor are in the Site Imaging Manual.

8.2.1.2 Tumor Imaging During the Substudy

The first on-study imaging assessment should be performed at 9 weeks (63 days $\pm$ 7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days $\pm$ 7 days) for the first year (until Week 52), after which the imaging interval increases to every 12 weeks (84 days $\pm$ 7 days) for ~2 years (until Week 104); and Q24W thereafter or sooner if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator per RECIST 1.1 unless the investigator elects to continue treatment and follow iRECIST, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the CIV.

Per iRECIST (Section 8.2.1.5), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of progressive disease in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 8.2.1.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study intervention. Exceptions are detailed in Section 8.2.1.5.

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation ($\pm$ 4-week window). If previous imaging was obtained within 4 weeks before the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks for the first year [through Week 52] and approximately every 12 weeks after Year 1) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of this substudy, whichever occurs first.

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg,

discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.2.1.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator. This allowance to continue treatment despite initial radiologic progressive disease takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study intervention at central verification of site-assessed first radiologic evidence of progressive disease and is not required to have repeat tumor imaging for confirmation of progressive disease by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm progressive disease by iRECIST, per investigator assessment. Images should continue to be sent to the central imaging vendor for potential retrospective BICR.

If repeat imaging does not confirm progressive disease per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule. If progressive disease is confirmed, participants will be discontinued from study intervention.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered after consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of

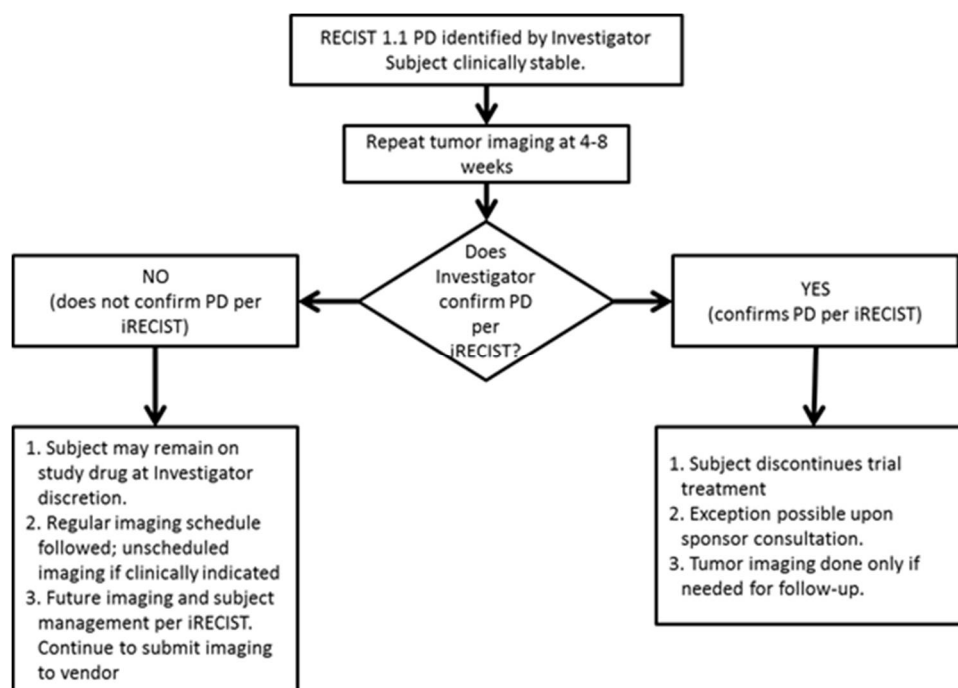
imaging and treatment requirements after first radiologic evidence of progression is provided in [Table 6](#) and illustrated as a flowchart in [Figure 2](#).

Table 6 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of progressive disease by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm progressive disease.	May continue study intervention at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm progressive disease per investigator's discretion only.	Discontinue treatment.
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable.
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm progressive disease. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm progressive disease per investigator's discretion only.	Discontinue treatment.
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression.

Figure 2 Imaging and Treatment for Clinically Stable Participants Treated With Investigational Agent(s) ± Pembrolizumab After First Radiologic Evidence of Progressive Disease Assessed by the Investigator



iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.

8.2.2 Quality of Life Assessments

Patient-reported outcomes will be assessed on Day 1 (before the first dose of study intervention) of every cycle, at the time of discontinuation (EOT visit), and the 30-day Safety Follow-up Visit. If the EOT visit occurs 30 days from the last dose of study intervention a Safety Follow-up Visit is not required and ePROs do not need to be repeated.

Every effort should be made to administer HRQoL surveys before administration of study intervention and before other assessments and procedures. Participants will complete the questionnaires in the following order: 1) EORTC QLQ-C30 and 2) EQ-5D-5L. If the participant does not complete the PROs at the designated time, the reason must be captured.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this substudy protocol are provided; refer to Appendix 11 for country-specific requirements. The total amount of blood/tissue to be drawn/collected over the course of this substudy (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual and vendor's collection flow chart.

The sites should submit tumor samples to the central pathology laboratory for adequacy of tumor tissue and for biomarker analysis.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at the timepoints specified in the SoAs (Appendix 6, Section 10.6.2.1). Height and weight will also be measured and recorded.

A brief directed physical examination including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

8.3.2 Vital Signs

The investigator or qualified designee will measure vital signs at the timepoints specified in the SoA (Appendix 6, Section 10.6.2.1). Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight will be monitored as per vital signs. Height will be measured at Screening only. Refer to Appendix 6, Section 10.6.2.19.1 for required vital signs assessments for specific investigational agents.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed during Screening using local standard procedures. Clinically important abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary. Refer to Appendix 6, Section 10.6.2.19.2 for required ECG assessments for specific investigational agents.

8.3.4 Multiple-gated Acquisition Scan or Echocardiogram

All participants will undergo a MUGA scan (using technetium-based tracer) or an ECHO at screening to assess LVEF (Appendix 6, Section 10.6.2.1). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality. Refer to Appendix 6 Section 10.6.2.19.3 for required MUGA or ECHO assessments for specific investigational agents.

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the substudy in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the substudy or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 Urine Dipstick

All participants will undergo urine dipstick testing at Screening (within 3 days before the administration of the first dose of study intervention); testing will be performed locally. Participants with >1+ proteinuria on urine dipstick at Screening will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥ 1 g/24-hr will not be eligible. Refer to Appendix 6, Section 10.6.2.19.4.1 for required urine dipstick testing for specific investigational agents.

8.3.6 Pregnancy Testing

All women who are being considered for participation in this substudy, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours before the first dose of study intervention. ^{CCI}



8.3.7 Performance Assessments

ECOG Performance Scale: The investigator or qualified designee will assess ECOG status (Appendix 10) at the timepoints specified in the SoA (Appendix 6, Section 10.6.2.1).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization/allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention randomization/allocation through 90 days following cessation of study intervention must be reported by the investigator or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention randomization/allocation through 120 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention randomization/allocation through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former substudy participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the substudy, and he/she considers the event to be reasonably related to the study intervention or substudy participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in [Table 7](#).

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	<u>Reporting Time Period:</u> Consent to Randomization/ Allocation	<u>Reporting Time Period:</u> Randomization/ Allocation Through Protocol-specified Follow-up Period	<u>Reporting Time Period:</u> After the Protocol- specified Follow-up Period	<u>Time Frame to Report Event and Follow-up Information to Sponsor:</u>
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer ^a and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

^a Progression of cancer under study is not reportable as per protocol-specified criteria (refer to Section 8.4.6).

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

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

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized/allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of 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 and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, 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 an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in this substudy. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7

CCI

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8.5

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8.6 CCI

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8.6.1 CCI

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8.6.2 CCI

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8.7 CCI

CCI

8.8 Patient-reported Outcomes

Refer to Section 8.2.2.

8.9 CCI

CCI

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- CCI
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8.9.1

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8.10 Future Biomedical Research Sample Collection

Not applicable.

8.11 Health Economics Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and substudy site personnel for all participants throughout this substudy. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- All-cause hospitalizations and emergency room visits, from the time of treatment randomization/allocation through 90 days after cessation of study intervention, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier.

8.12 Visit Requirements

Visit requirements are outlined in Appendix 6, Section 10.6.2.1. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Documented informed consent must be obtained before performing any protocol-specific procedure. Results of a test performed before the participant providing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days before the first dose of study intervention except for the following:

- Laboratory tests (hematology, chemistry, and urinalysis) are to be performed within 7 days before the first dose of study intervention. An exception is hepatitis and HIV testing which may be done up to 28 days before the first dose of study intervention if mandated by local health authorities (see [Table 10](#) in Appendix 2).

- Evaluation of ECOG performance status is to be performed within 7 days before the first dose of study intervention.
- Full physical examination is to be performed within 7 days of the first dose of study intervention.
- 12-lead ECG is to be performed within 7 days before the first dose of study intervention.
- Any additional procedure or assessment for specific investigational agents, which will also be required at Screening for all participants (see Appendix 6, Section 10.6.2.1.1).
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours before the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local substudy site laboratory).
- An archival tumor sample should have been collected within the interval from completion of last treatment and before entering the Screening Period. Newly obtained tumor tissue may be obtained within 90 days of the first dose of study intervention. The sites should submit tumor samples to the central pathology laboratory for adequacy of tumor tissue and for biomarker analysis.

8.12.1.1 Rescreening

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial Screening Period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.12.2 Treatment Period

Visit requirements are outlined in the SoA. Specific procedure-related details are provided in Section 8.

8.12.3 Discontinued Participants Continuing to be Monitored in This Substudy

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed combined. Visit requirements are outlined in the SoA. Additional details regarding participant withdrawal and discontinuation are presented in Section 8.1.9.

8.12.4 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

8.12.5 Imaging Follow-up Visit(s)

Participants who discontinue treatment for reasons other than documented progressive disease should continue with imaging assessments per the protocol defined schedule until: (1) progressive disease is documented, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, or (5) substudy conclusion or early termination, whichever occurs first.

8.12.5.1 Follow-up Visits

Participants who discontinue study intervention for a reason other than disease progression will move into the Follow-up Phase and should be assessed every 9 weeks (63 days $\pm$ 7 days) for ~1 year (until Week 52), then every 12 weeks (84 days $\pm$ 7 days) for ~2 years (until Week 104); and Q24W thereafter or sooner if clinically indicated. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of substudy. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

8.12.5.2 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of this substudy, whichever occurs first.

8.12.6 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during this substudy by the Sponsor. For example, updated survival status may be requested prior to but not limited to an internal DMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled substudy visit or substudy contact during the Sponsor-defined time period will be contacted for their survival status.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section outlines the statistical analysis strategies and procedures for the primary analyses of this substudy. CC

If, after this substudy has begun, changes are made to the primary objectives, or to the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). ^{CCI}

Full details are in the SAP, Section 9.6.

Study Design Overview	A Phase 1/2 Open-label, Rolling-arm, Umbrella Platform Design of Investigational Agents With or Without Pembrolizumab or Pembrolizumab Alone in Participants with Melanoma (KEYMAKER-U02): Substudy 02A This substudy protocol includes participants with PD-1 refractory melanoma.
Treatment Assignment	This is an open-label substudy. Participants will be randomized ^{CCI}
Analysis Populations	Efficacy: • APaT Safety: • APaT
Primary Endpoints	• ORR as assessed by BICR per RECIST 1.1. • AEs and study intervention discontinuations due to AEs.
Secondary Endpoint(s)	DOR as assessed by BICR per RECIST 1.1.
Statistical Methods for Efficacy Analyses	^{CCI}
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

9.4.1.1 Primary

- **Objective Response Rate (ORR)**

The ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR. Participants without follow-up scans will be considered nonresponders. ORR as assessed by investigator per RECIST 1.1 and iRECIST are considered exploratory endpoints.

9.4.1.2 Secondary

- **Duration of Response (DOR)**

For participants who show confirmed CR or PR per RECIST 1.1 as assessed by BICR, duration of response is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

9.4.1.3

CCI

CCI

9.4.2 Safety Endpoints

The safety endpoints include AEs, SAEs, and study intervention discontinuation due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. A description of safety measures is provided in Section 8.3.

9.4.3

CCI

CCI

- CCI

- CCI [REDACTED]

CCI [REDACTED]

9.4.4 CCI [REDACTED]

CCI [REDACTED]

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

CCI [REDACTED]

9.5.2 Safety Analysis Population

CCI [REDACTED]

9.5.3 PRO Analysis Populations

CCI [REDACTED]

9.5.4 Pharmacokinetic Analysis Populations

CCI [REDACTED]

CCI

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. CCI. This is an estimation substudy. The primary and secondary endpoints will be summarized for each investigational treatment arm separately. Formal hypothesis tests will not be conducted.

9.6.1 Statistical Methods for Efficacy Analysis

9.6.1.1 Objective Response Rate (ORR)

CCI

9.6.1.2 Duration of Response (DOR)

CCI

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, and ECG measurements. CCI

Details of the DLT analysis will be documented in the sSAP.

9.6.3 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized.

9.6.4

CCI

9.7

CCI

CCI

CCI

9.8 Multiplicity

CCI

9.9 Sample Size and Power Calculations

The base study with a total of 40 participants

CCI

[Table 9](#) below shows the 2-sided 90% and 95% CIs of ORR with 40 participants (at the end of the base study) and 100 participants (at the end of the expansion study) (N = 100) for different observed ORRs based on the method of Clopper and Pearson [Clopper, C. J. 1934].

Table 9

CCI

CCI

9.10 Subgroup Analyses

To determine whether the response rate is consistent across various subgroups, the estimate of ORR (with a nominal 90% CI) endpoint will be estimated within each category of the following classification variables:

- CCI
- CCI
- CCI

CCI

9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during this substudy. Any deviation from protocol-directed administration will be reported. If there are oral medications in the respective treatment arm, details of the compliance definition will be provided according in the sSAP.

9.12 Extent of Exposure

The extent of exposure will be evaluated by summary statistics for duration of treatment.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

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

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

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1

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CCI

10.1.4.2

CCI

CCI

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will

review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 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

or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

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

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

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

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 review and 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 participants' documented informed consent, 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.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 10](#) will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively, and Appendix 6, Section 10.6.2.7 and Section 10.6.2.8 of this substudy protocol.
- Additional tests may be performed at any time during this substudy as determined necessary by the investigator or required by local regulations.
- Pregnancy testing (lenvatinib):
 - Pregnancy testing requirements for study inclusion are described in Section 5.1.
 - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
 - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
 - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: MCV ^c MCH ^c %Reticulocytes ^c		WBC count with Differential ^{1a} : Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count			
	Hemoglobin			
	Hematocrit			
Chemistry	BUN ^b	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate ^c	Chloride ^c	Phosphorus ^c
	Creatinine ^d	Sodium	ALT/SGPT	Total Protein ^c
	Glucose	Calcium	Alkaline phosphatase	Magnesium
	TSH	Free thyroxine ^e	Serum LDH ^c	Amylase
	Lipase	Cholesterol ^c	Triglycerides ^c	CPK ^f
	Pregnancy test	Triiodothyronine (Total T3) ^e		
Routine Urinalysis ^g	• Specific gravity • pH, glucose, protein, hemoglobin or blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• PT/INR and aPTT/PTT^h. • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) NOTE: certain ex-US sites require testing for HIV and hepatitis B and C during screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable. • Serum or urine β hCG pregnancy test (as needed for WOCBP). • Coagulation factors (PT or INR and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.			

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin; AST=aspartate aminotransferase; β hCG=β human chorionic gonadotropin; BUN=blood urea nitrogen; CPK=creatine phosphokinase; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; RNA=ribonucleic acid; LDH=lactate dehydrogenase; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin, PT/INR=prothrombin time/international normalize ratio; PTT=partial prothrombin time; RBC=red blood cell; SGOT=serum glutamic pyruvic transaminase; WBC=white blood cell count; WOCBP=women of childbearing potential; T3=triiodothyronine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal

^a Absolute or % acceptable per institutional standard.

^b Urea is acceptable if BUN is not available as per institutional standard.

^c Performed only if considered local standard of care. Serum LDH at Screening is required.

^d GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.

^e Free T4, Total T3, and TSH levels will be performed during screening, at cycles specified in the SoA, and at the time of discontinuation (End of Treatment). Free T3 is acceptable where Total T3 cannot be determined. There may be instances when sites are unable to obtain thyroid function testing results before the scheduled dosing. After C1, retrospective review of thyroid function testing results after dosing is acceptable.

^f CPK isoenzymes (CK-MB) should be evaluated if CPK is greater than 3 × ULN.

^g If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution’s laboratory.

^h Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulation therapy.

The investigator (or medically qualified designee) 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 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 a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

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.

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

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant’s medical history.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE:

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose.

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

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

Assessment of intensity/toxicity

- 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.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
 - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
 - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
 - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
 - Grade 4: Life threatening consequences; urgent intervention indicated.
 - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor’s product cause the AE?
- The determination of the likelihood that the Sponsor’s product caused the AE will be provided by an investigator who is a qualified physician. The investigator’s signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor’s product and the AE; the greater the correlation with the components and**

their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
 - If yes, did the AE resolve or improve?
 - If yes, this is a positive dechallenge.
 - If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
 - If yes, did the AE recur or worsen?
 - If yes, this is a positive rechallenge.
 - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
 - Yes, there is a reasonable possibility of Sponsor's product relationship:
 - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
 - No, there is not a reasonable possibility of Sponsor's product relationship:
 - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- 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 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
 - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
 - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
 - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women 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 first dose of study intervention, additional evaluation should be considered.

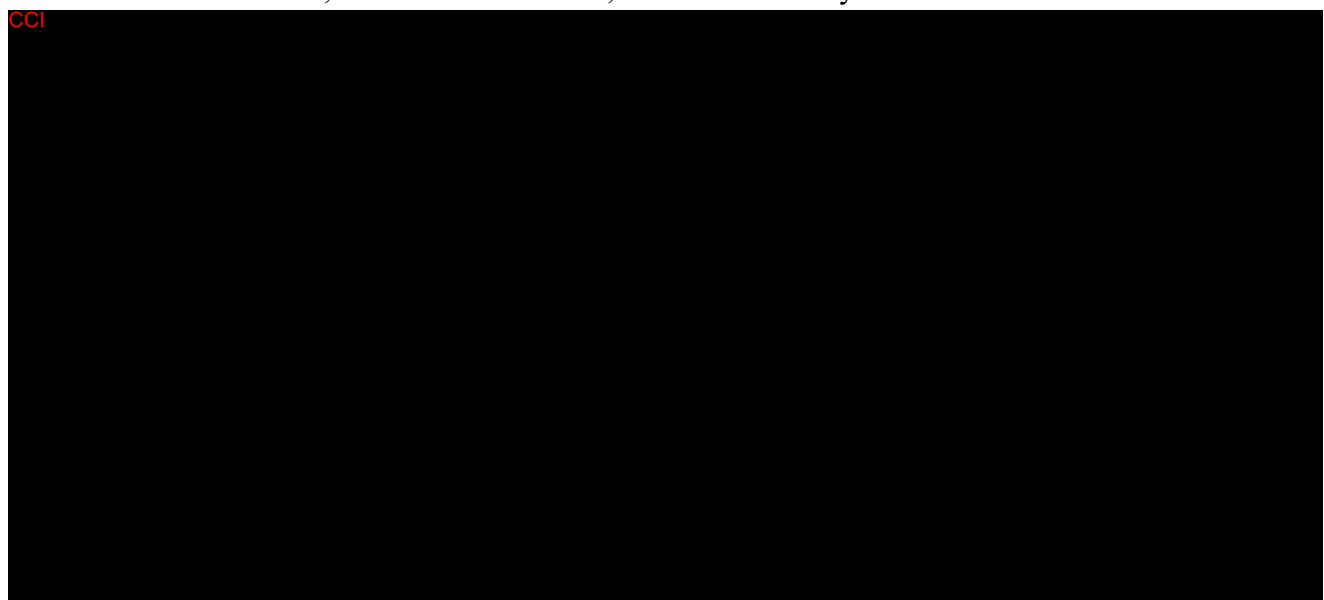
Women in the following categories are not considered WOCBP:

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

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

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

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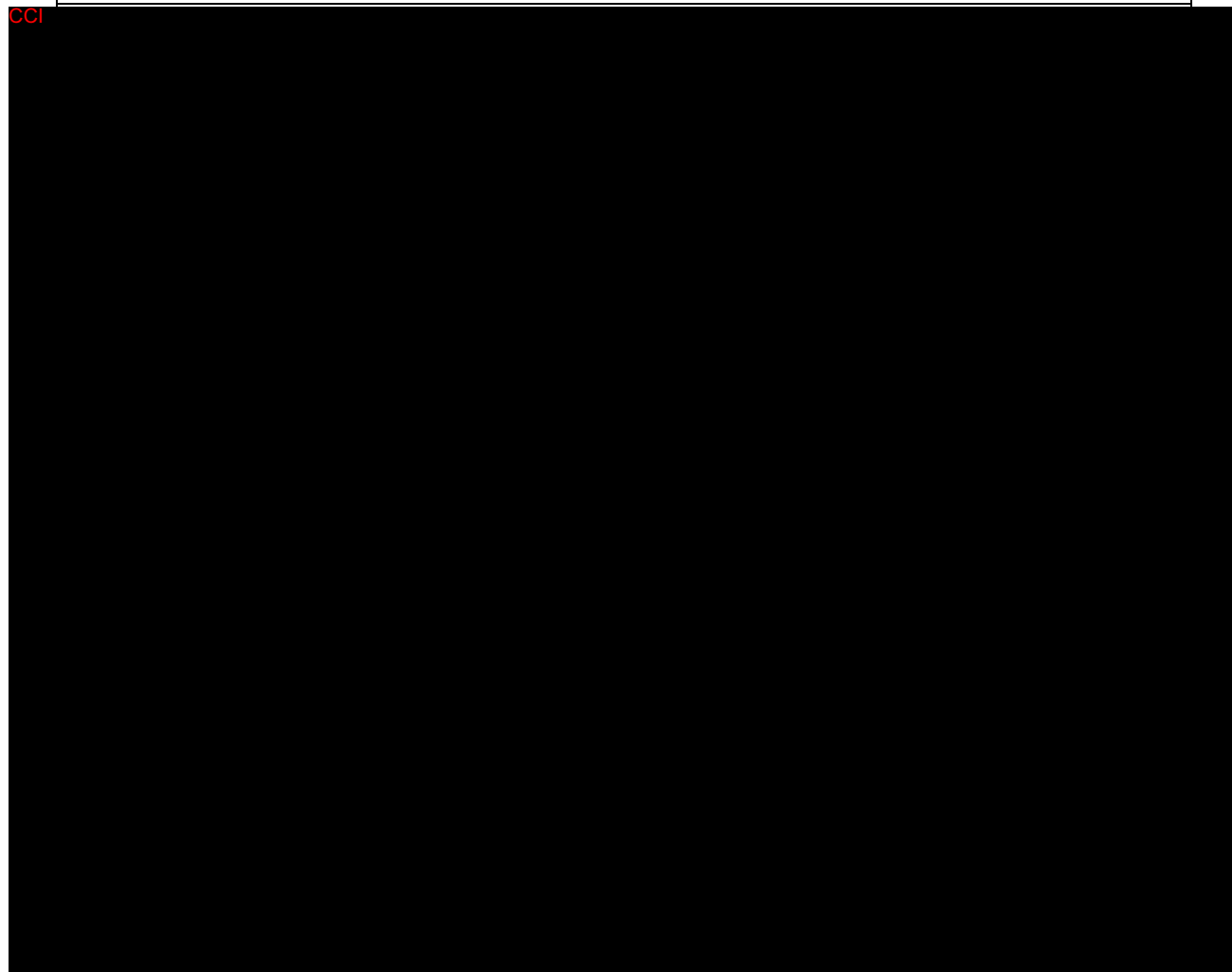


10.5.2 Contraception Requirements

Female Participants

Contraceptives allowed during the study include ^a :
Highly Effective Contraceptive Methods That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i>

CC



10.6 Appendix 6: Substudy Combination-specific Requirements

10.6.1 Status of Investigational Agents in this Substudy Protocol

Table 11 Summary of Investigational Agents Activated for Randomization/Allocation

Investigational Agent	Active Investigational Treatment Arms	Dosing Schedule	Section
MK-1308	Arm 1 and Arm 2	25 mg q6w	10.6.2
MK-7684 (anti-TIGIT)	Arm 1	200 mg q3w	10.6.2
Lenvatinib	Arm 2	20 mg once daily	10.6.2
ATRA	Arm 3	75 mg/m ² , twice daily for 3 days q3w (Total dose of 150 mg/m ² per day for 3 days)	10.6.2

Table 12 Summary of Investigational Agents No Longer Activated for Randomization/Allocation

Investigational Agent	Inactive Investigational Treatment Arms	Dosing Schedule	Section
Lenvatinib	Arm 2	20 mg once daily	10.6.2
-	-	-	-

Investigational Treatment Arm 1: Pembrolizumab 200 mg q3w IV + MK-1308 25 mg q6w IV + MK-7684 200 mg q3w IV. Treatment period is approximately 2 years. The SoAs described in Section 1.3.1 and Section 1.3.2 of this appendix should be followed.

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Investigational Treatment Arm 2: Pembrolizumab 400 mg q6w IV + MK-1308 25 mg q6w IV + lenvatinib 20 mg qd PO. Treatment period is approximately 2 years. The SoAs described in Section 1.3.1 and Section 1.3.3 of this appendix should be followed.

CCI [REDACTED]

Investigational Treatment Arm 3: Pembrolizumab 400 mg q6w IV + 75 mg/m² ATRA twice daily (total daily dose: 150 mg/m²) for 3 days PO q3w. Treatment period is approximately 2 years. The SoAs described in Section 1.3.1 and Section 1.3.4 of this appendix should be followed.

10.6.2 Investigational Agent Information Summary

Procedures and assessments specific for MK-7684, MK-1308, lenvatinib, and ATRA are detailed in the following sections. Refer to the main body of the protocol for general aspects that govern the overall conduct of this substudy.

Note: Within this appendix, the subsections that follow correspond 1:1 with those in the main body of the protocol.

10.6.2.1 Section 1.3 Schedule of Activities

10.6.2.1.1 Section 1.3.1 Screening

Study Period	Screening (Applicable to all Participants in Substudy 2A)	Notes
Visit Timing/Cycle Number	-28 to -1	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for Visit Requirements.
Cycle Day		
Scheduling Window (Days)	-28 to -1	
Administrative Procedures		
Informed consent	X	Informed consent can be provided at any time before any protocol-specific screening procedures being performed. Additional consent is required at disease progression.
Inclusion/exclusion criteria	X	
Participant identification card	X	
Medical/surgical history	X	Significant medical/surgical history will be captured for last 10 years.
Demographics	X	
Staging	X	At initial diagnosis and at study entry (assessed during Screening).
BRAF status	X	BRAF V600 mutation analysis should be performed locally by the sites during Screening in participants without documented BRAF status. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central pathology laboratory for testing.
Prior and concomitant medication review	X	
Efficacy/Immunogenicity Procedures		
Prestudy imaging	X	The site’s study team must have reviewed prestudy images to determine that radiographic progression has occurred per RECIST 1.1 and iRECIST after initiation of the anti-PD-1/L1 agent.

Study Period	Screening (Applicable to all Participants in Substudy 2A)	Notes
Visit Timing/Cycle Number	-28 to -1	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for Visit Requirements.
Cycle Day		
Scheduling Window (Days)	-28 to -1	
Tumor assessment: chest, abdomen, and pelvis (CT/MRI)	X	Scans performed within the Screening Period but before signing the ICF may be used if consistent with protocol requirements per SIM. Investigators must receive verification of measurable disease by BICR before randomization/allocation. Imaging of any anatomy that shows disease at Screening or in subsequent evaluations will be required and should be submitted to the CIV. All imaging visits have a scheduling window of ± 7 days. If additional time is needed for initial image submission and CIV diagnostic quality review, an extension of the screening window of up to 7 days may be approved after mandatory Sponsor consultation. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET-CT may be used in place of a stand-alone CT if it is of diagnostic quality per Site Imaging Manual.
Digital photography	X	Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the CIV.
Brain MRI	X	A brain MRI is required at Screening. Brain CT scan should only be used when MRI is contraindicated.
Safety Procedures		
AE monitoring	X	Record AEs if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention (eg, procedure).
Complete physical examination	X	To be performed within 7 days of first dose of study intervention.
Vital signs (resting BP, heart rate, RR, and temp), weight, and height	X	Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 for vital signs and Section 8.3.2 of this appendix for vital signs for specific investigational agents, which is required at Screening for all participants. Height is measured at Screening only.
12-lead ECG	X	Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes before the ECG. Additional assessments may be performed if clinically indicated. To be performed within 7 days of first dose of study intervention. See Section 8.3.3 for ECG and Section 8.3.3 of this appendix for ECG for specific investigational agents, which is required at Screening for all participants.

Study Period	Screening (Applicable to all Participants in Substudy 2A)	Notes
Visit Timing/Cycle Number	-28 to -1	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for Visit Requirements.
Cycle Day		
Scheduling Window (Days)	-28 to -1	
MUGA or ECHO for LVEF assessment	X	Additional assessments may be performed as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the substudy. See Section 8.3.4 of this appendix for MUGA or ECHO for specific investigational agents, which is required at Screening for all participants.
Hematology and chemistry laboratory assessment	X	Screening samples collected within 7 days of first dose of study intervention. Serum LDH is required at Screening. Includes CBC and differential.
Urinalysis	X	Screening samples collected within 7 days of first dose of study intervention. Additional assessments may be performed if clinically indicated.
Urine dipstick testing	X	Performed locally within 3 days of first dose of study intervention. Participants with >1+ proteinuria on urine dipstick at Screening will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥ 1 g/24-hr will not be eligible. See Section 8.3.5.1 of this appendix for dipstick testing for specific investigational agents, which is required at Screening for all participants.
PT/INR and aPTT/PTT	X	Screening samples collected within 7 days of first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
T3, FT4, TSH	X	Screening samples to be collected within 7 days of first dose of study intervention. Free T3 is acceptable where Total T3 cannot be determined.
Pregnancy test (WOCBP only)	X	To be assessed within 24 hours before the first dose of study intervention. If more than 24 hours have elapsed before first dose of study intervention, another pregnancy test is required before starting study intervention. A serum or urine pregnancy test will be performed as indicated, before first dose of study intervention. See Appendix 11 for country-specific guidelines. See Section 8.3.6 of this appendix for pregnancy testing for specific investigational agents, which is required at Screening for all participants.
Serum FSH or estradiol	X	Only for women <45 years old with no menses for ≥ 1 year (12 months) and not currently on HRT or hormonal contraception.
HIV, HBV, HCV	X	Testing is not required unless mandated by local health authorities.
ECOG performance status	X	To be assessed within 7 days of first dose of study intervention.

Study Period	Screening (Applicable to all Participants in Substudy 2A)	Notes
Visit Timing/Cycle Number	-28 to -1	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for Visit Requirements.
Cycle Day		
Scheduling Window (Days)	-28 to -1	
Biomarkers		
Tumor blocks or slides	X	Collected during Screening for adequacy of tumor tissue at a central pathology laboratory. PD-L1 IHC testing will be performed centrally but does not need to be completed during Screening. See Section 8.9 for details on biomarker assessments.

AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; BRAF=v-raf murine sarcoma viral oncogene homolog B1; C1=Cycle 1; CIV=central imaging vendor; CT=computed tomography; D1=Day 1; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; FSH=follicle stimulating hormone; FT4=free thyroxine; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRT=hormone replacement therapy; ICF=Informed Consent Form; IHC=immunohistochemistry; INR=international normalized ratio; LDH=lactate dehydrogenase; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PD-1/L1=programmed cell-death 1/programmed cell-death ligand 1; PET-CT=positron emissions tomography-computed tomography; PT=prothrombin time; PTT=partial thromboplastin time; RR=respiratory rate; SIM=Site Imaging Manual; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

10.6.2.1.2 Section 1.3.2 Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Administrative Procedures													
Concomitant medication review	X	X	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).
Randomization/ allocation	X												Participants may be randomized/allocated up to 24 hours before first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/allocation.
Dispensation of pembrolizumab drug kit	X			X			X						Day 1 of every cycle (eg, C1D1, C2D1, C3D1, etc.)
Pembrolizumab administration	X			X			X						Pembrolizumab will be administered q3w for up to 2 years of treatment.
Dispensation of MK-7684 drug kit	X			X			X						Day 1 of every cycle (eg, C1D1, C2D1, C3D1, etc.)

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days						EOT ^c	Posttreatment				Notes	
								Safety ^c	Follow-up ^d		Survival		
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
MK-7684 administration	X			X			X						MK-7684 will be administered q3w for up to 2 years of treatment.
Dispensation of MK-1308 drug kit	X						X						Day 1 of every other cycle (eg, C1D1, C3D1, C5D1, etc.)
MK-1308 Administration	X						X						MK-1308 will be administered q6w (ie, every other cycle) for up to 2 years of treatment.
Subsequent antineoplastic treatment									X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
DLT window	←-----→												The DLT window is defined as 1 cycle from first dose of study intervention.
Survival status	←-----→												Participants may be contacted for survival status at any time during the course of this substudy.

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a														
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes	
									Safety ^c	Follow-up ^d		Survival		
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.	
Cycle Day	1	8	15	1	8	15	1							
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7		
Efficacy/Immunogenicity Procedures														
Tumor assessment: chest, abdomen, and pelvis (CT/MRI) ^e	←-----→							X		X	X		All imaging visits have a scheduling window of ±7 days. See Section 8.2.1 Tumor Imaging and Assessment of Disease. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of a stand-alone CT if it is of diagnostic quality per Site Imaging Manual.	
Digital photography	←-----→													Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Safety Procedures													
AE monitoring	X	X	X	X	X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Directed physical examination	X		X	X		X	X	X	X				In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during this substudy, as clinically indicated.
Vital signs (resting BP, heart rate, RR, and temp), and weight	X	X	X	X		X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 and Section 8.3.2 of this appendix for vital signs.
12-lead ECG	←-----→												As clinically indicated. Participants must be in the recumbent position for a period of 5 minutes before the ECG. See Section 8.3.3 for ECG.

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Hematology and chemistry laboratory assessment	X	X	X	X		X	X	X	X				Procedures/assessments should be performed before all scheduled substudy visits. Every effort should be made to collect samples at the same time of day.
Urinalysis	←-----→												As clinically indicated.
PT/INR and aPTT/PTT	←-----→												As clinically indicated for participants taking anticoagulant therapy.
T3, FT4, TSH				X			X	X					Thyroid function tests will be performed at Cycle 2 and every other cycle thereafter (eg, C4, C6, etc.) and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1, retrospective review of thyroid function testing results is allowed when the results are not available before dosing.

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Pregnancy test (WOCBP only)				X			X	X	X	X			To be assessed before all scheduled visits. A serum or urine pregnancy test will be performed as indicated, before every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.
ECOG performance status				X			X	X	X				To be assessed before dosing during all scheduled visits.
Patient-reported Outcomes													
EORTC QLQ-30	X			X			X	X	X				Patient-reported outcomes will be assessed on Day 1 (before first dose of study intervention) of every cycle, at the Discontinuation Visit, and the 30-day Safety Follow-up Visit. If the EOT visit occurs 30 days from the last dose of study intervention, a 30-day required Safety Follow-up Visit is not required. ePROs do not need to be repeated. See additional details in Section 8.2.2.
EQ-5D-5L	X			X			X	X	X				

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Pharmacokinetics/Pharmacodynamics/Biomarkers													
CCI	X						X	X	X				Predose Day 1 at Cycles 1, 3, 5, and 7 and every 4 cycles thereafter. CCI CCI CCI

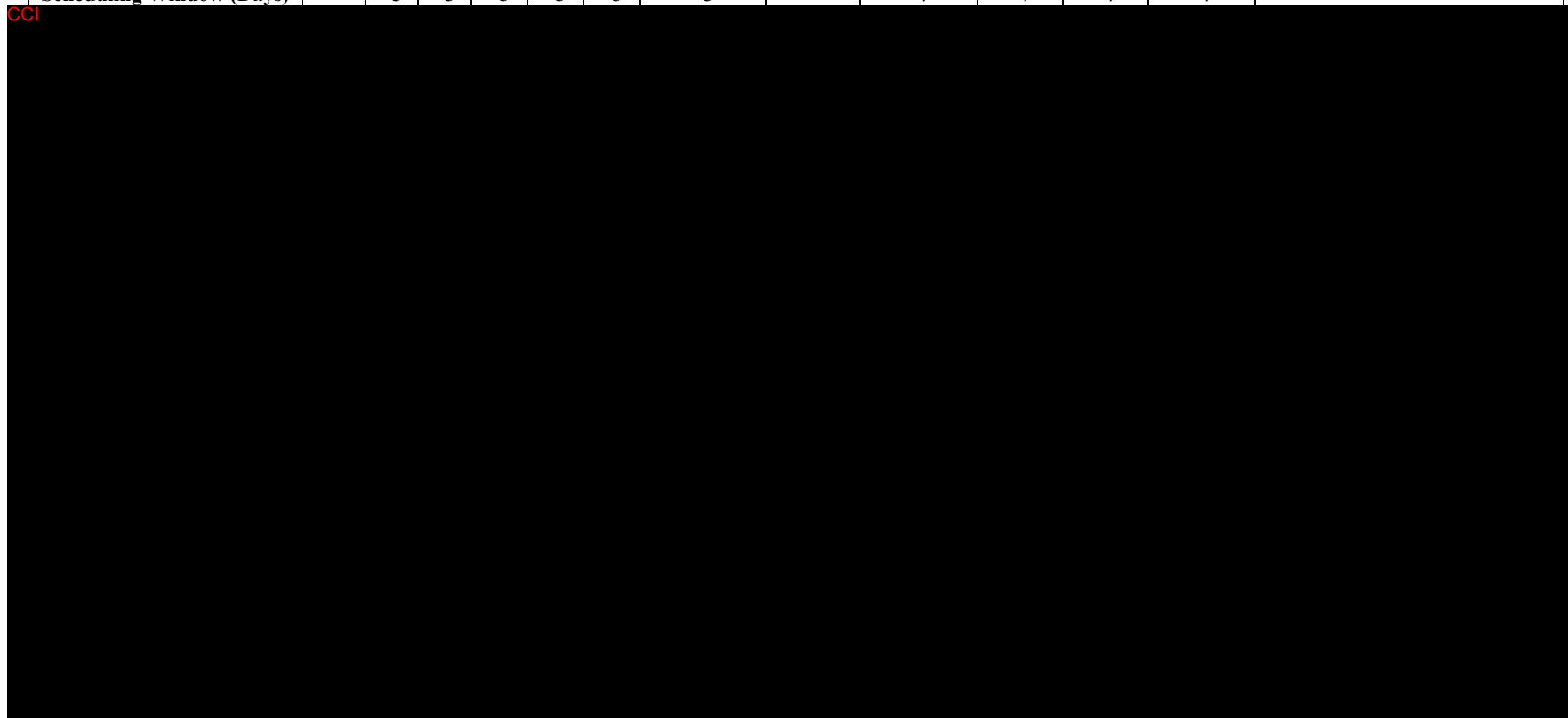
Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
CCI	X						X	X	X				Predose Day 1 of Cycles 1, 3, 5, and 7 and every 4 cycles thereafter. CCI
													CCI

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
CCI	X						X	X	X				Predose Day 1 at Cycles 1, 3, 5, and 7 and every 4 cycles thereafter. CCI

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
CCI	X						X	X	X				Predose Day 1 of Cycles 1, 3, 5 and 7 and every 4 cycles thereafter. CCI
													CCI

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
CCI	X						X	X	X				Predose Day 1 at Cycles 1, 3, 5, and 7 and every 4 cycles thereafter. CCI CCI CCI
CCI	X						X	X	X				Predose Day 1 of Cycles 1, 3, 5, and 7 and every 4 cycles thereafter. CCI

Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	



Pembrolizumab + MK-7684 (anti-TIGIT) + MK-1308 (SoA applicable to participants in the Safety Lead-In and Efficacy Phase) ^a													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	

CCI

ADA=antidrug antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; C1=Cycle 1; C2=Cycle 2; C3=Cycle 3; C4=Cycle 4; C5=Cycle 5; C6=Cycle 6; CIV=central imaging vendor; CT=computed tomography; ctDNA=circulating tumor DNA; ctRNA=circulating tumor RNA; D1=Day 1; D8=Day 8; D15=Day 15; D/C=discontinue/discontinuing; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT=end of treatment; ePRO=electronic patient-reported outcome; EQ-5D-5L=European Quality of Life 5-dimension 5- level; FT4=free thyroxine; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRQoL=health-related quality of life; ICF=Informed Consent Form; INR=international normalized ratio; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PE=physical examination; PET=positron emission tomography; PK=pharmacokinetics; PT=prothrombin time; PTT=partial thromboplastin time; q3w=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; qd=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; SIM=Site Imaging Manual; SoA=Schedule of Assessments; T3=triiodothyronine; TSH=thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP=women of childbearing potential.

- a This SoA is also applicable to MK-7684 + pembrolizumab alone, whereby if enrollment expands to 10 participants for a dose level and >4/10 participants develop a DLT, enrollment will continue with MK-7684 + pembrolizumab alone. As this combination dose has previously shown tolerability in patients with advanced solid tumors (see MK-7684 IB), these participants will follow the Efficacy Phase of this substudy without a Safety Lead-in Phase.
- b Participants who attain an investigator-determined complete response (CR) and stop study intervention will have 30-day Safety Follow-up Visit and move to the follow-up visits per SoA.
- c If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up Visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up Visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.
- d For participants who D/C study intervention for reasons other than progressive disease, follow-up visits to monitor disease status continue until progressive disease or initiation of a new anticancer therapy. Participants who D/C study intervention due to progressive disease will proceed directly to Survival Follow-up.
- e A brain MRI must be performed at Screening for all participants. For participants with brain metastasis at Screening, brain MRI should then be performed Q9W until Week 52 of study intervention and Q12W thereafter until Week 104; after Week 104, imaging should be performed every Q24W, or sooner if clinically indicated. A brain MRI at EOT is required. Brain CT scan should only be used when MRI is contraindicated. The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden.

CCI

10.6.2.1.3 Section 1.3.3 Pembrolizumab + MK-1308 + Lenvatinib

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Administrative Procedures													
Concomitant medication review	X	X	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).
Randomization/ allocation	X												Participants may be randomized/allocated up to 3 days before first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/allocation.
Dispensation of pembrolizumab drug kit	X						X						Day 1 of every other cycle (eg, C1D1, C3D1, C5D1, etc.).
Pembrolizumab administration	X						X						Pembrolizumab will be administered q6w (ie, every other cycle) for up to 2 years of treatment.
Dispensation of MK-1308 drug kit	X						X						Day 1 of every other cycle (eg, C1D1, C3D1, C5D1, etc.)

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
MK-1308 administration	X						X						MK-1308 will be administered q6w (ie, every other cycle) for up to 2 years of treatment.
Dispensation of lenvatinib drug kit	X			X			X						Day 1 of every cycle (eg, C1D1, C2D1, C3D1, etc.) Note: Dose reductions of lenvatinib in the middle of a cycle will be allowed.
Lenvatinib administration	X	X	X	X	X	X	X						Lenvatinib will be administered daily on a 21-day cycle for up to 2 years of treatment. On C1D1, C2D1, C3D1, etc, lenvatinib will be taken 0-4 hours after completion of pembrolizumab and MK-1308 administration, if applicable. Lenvatinib will be taken in the clinic on C1D1, C2D1, C3D1, etc. Participants may be allowed to continue lenvatinib beyond 2 years, at the investigator’s discretion, if there is clinical benefit.

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Subsequent antineoplastic treatment									X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
DLT window	↔												The DLT window is defined as 1 cycle from first dose of study intervention. The DLT window will only be applicable to participants in the Safety Lead-in Phase.
Survival status	←-----→												Participants may be contacted for survival status at any time during the course of this substudy.

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Efficacy/Immunogenicity Procedures													
Tumor assessment: chest, abdomen, and pelvis (CT/MRI) ^d	←-----→							X		X	X		All imaging visits have a scheduling window of ±7 days. See Section 8.2.1 Tumor Imaging and Assessment of Disease. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of a stand-alone CT if it is of diagnostic quality per Site Imaging Manual.
Digital photography	←-----→												Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Safety Procedures													
AE monitoring	X	X	X	X	X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Directed physical examination	X		X	X		X	X	X	X				In addition to the directed PEs in the flowchart, a symptom- directed PE may be performed at any time during this substudy, as clinically indicated.
Vital signs (resting BP, heart rate, RR, and temp), and weight	X	X	X	X		X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 and Section 8.3.2 of this appendix for vital signs.

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
12-lead ECG	X			X			X	X	X				Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes before the ECG. Additional assessments may be performed if clinically indicated. ECG at screening, C1D1, C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and Safety Follow-up. At C1D1 and C2D1 only, an additional 2h-post-lenvatinib dose ECG is required. For high-risk patients (as defined in Section 8.3.3 of this appendix), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.

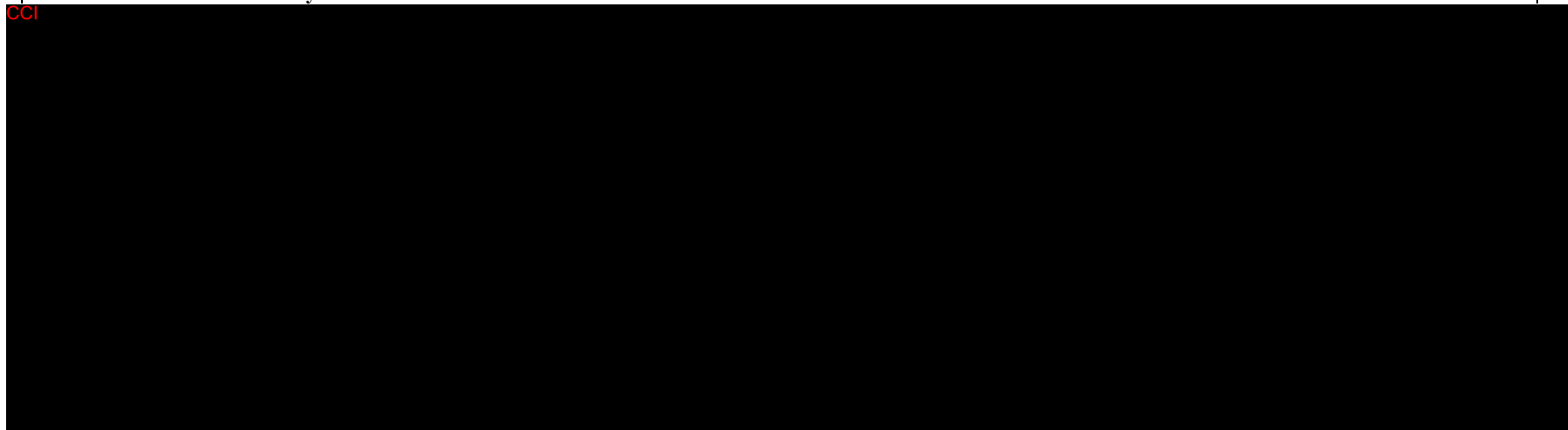
Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
MUGA or ECHO for LVEF assessment								X					Additional assessments as clinically indicated. Assessments should be performed locally and in accordance with the institution’s standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant.
Hematology and chemistry laboratory assessment	X	X	X	X		X	X	X	X				Procedures/assessments should be performed before all scheduled substudy visits. Every effort should be made to collect samples at the same time of day.
Urinalysis	←-----→												As clinically indicated.
PT/INR and aPTT/PTT	←-----→												As clinically indicated for participants taking anticoagulant therapy.

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Urine dipstick testing			X	X		X	X	X	X				Performed locally before all scheduled visits. See Section 8.3.5.1 of this appendix for dipstick testing.
T3, FT4, TSH				X			X	X					Thyroid function tests will be performed at Cycle 2 and every other cycle thereafter (eg, C4, C6, etc.), and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1, retrospective review of thyroid function testing results is allowed when the results are not available before dosing.
Pregnancy test (WOCBP only)				X			X	X	X	X			To be assessed before all scheduled visits. A serum or urine pregnancy test will be performed as indicated, before every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)														
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes	
									Safety ^b	Follow-up ^c		Survival		
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.	
Cycle Day	1	8	15	1	8	15	1							
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7		
ECOG performance status				X			X	X	X				To be assessed before dosing during all scheduled visits.	
Patient-reported Outcomes														
EORTC QLQ-30	X			X			X	X	X				Patient-reported outcomes will be assessed on Day 1 (before first dose of study intervention) of every cycle, at the Discontinuation Visit, and the 30-day Safety Follow-up Visit. If the EOT visit occurs 30 days from the last dose of study intervention, a 30-day required Safety Follow-up Visit is not required. ePROs do not need to be repeated. See additional details in Section 8.2.2.	
EQ-5D-5L	X			X			X	X	X					

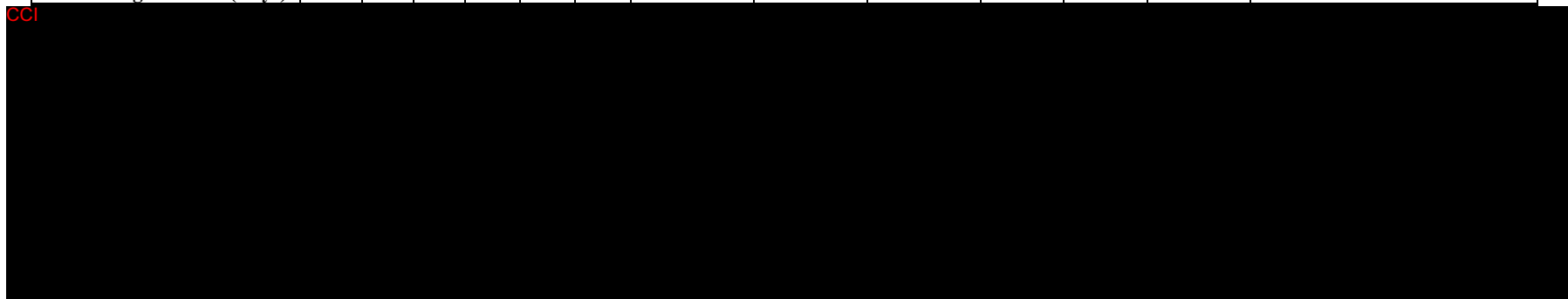
Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Pharmacokinetics/Pharmacodynamics/Biomarkers													

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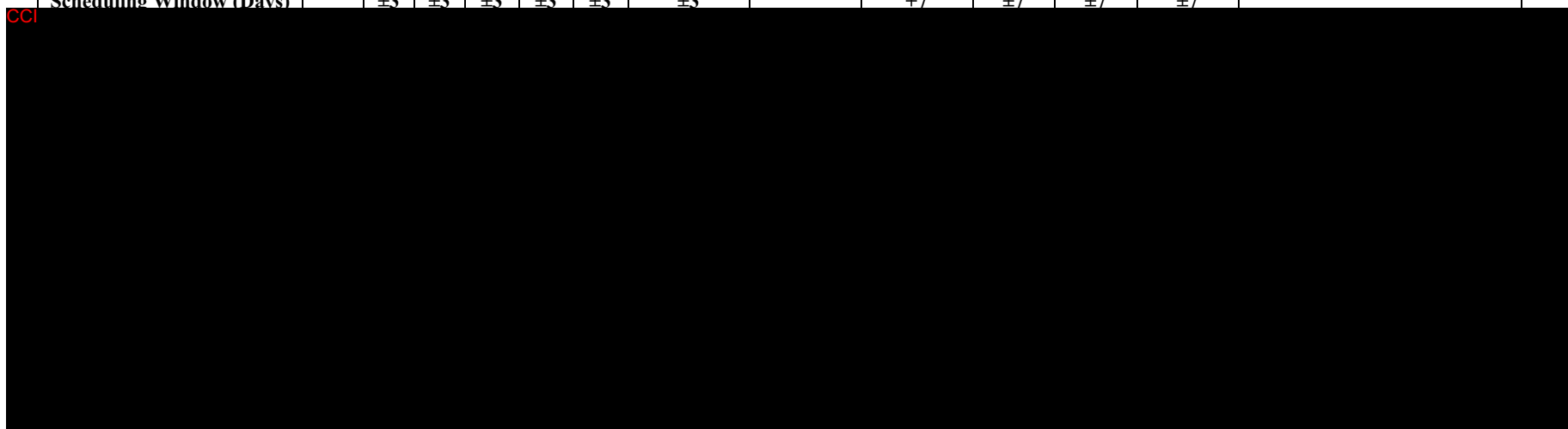


Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	

CCI



Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	



Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	

CCI

Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	

CCI

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Pembrolizumab + MK-1308 + Lenvatinib (SoA applicable to participants in the Safety Lead-In and Efficacy Phase)													
Study Period	Treatment Cycle = 21 days							EOT ^b	Posttreatment				Notes
									Safety ^b	Follow-up ^c		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^a	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	

CCI

ADA=antidrug antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; C1=Cycle 1; C2=Cycle 2; C3=Cycle 3; C4=Cycle 4; C5=Cycle 5; C6=Cycle 6; C10=Cycle 10; C14=Cycle 14; CIV=central imaging vendor; CT=computed tomography; ctDNA=circulating tumor DNA; ctRNA=circulating tumor RNA; D1=Day 1; D8=Day 8; D15=Day 15; D/C=discontinue/discontinuing; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT=end of treatment; ePRO=electronic patient-reported outcome; EQ-5D-5L=European Quality of Life 5-dimension 5- level; FT4=free thyroxine; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRQoL=health-related quality of life; ICF=Informed Consent Form; INR=international normalized ratio; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PE=physical examination; PET=positron emission tomography; PK=pharmacokinetics; PT=prothrombin time; PTT=partial thromboplastin time; q6w=every 6 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; qd=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; SIM=Site Imaging Manual; SoA=schedule of assessments; T3=triiodothyronine; TSH=thyroid-stimulating hormone; UPCr=urine protein-to-creatinine; WOCBP=women of childbearing potential.

- a Participants who attain an investigator-determined complete response (CR) and stop study intervention will have 30-day Safety Follow-up Visit and move to the follow-up visits per SoA.
- b If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up Visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up Visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.
- c For participants who D/C study intervention for reasons other than progressive disease, follow-up visits to monitor disease status continue until progressive disease or initiation of a new anticancer therapy. Participants who D/C study intervention due to progressive disease will proceed directly to Survival Follow-up.
- d A brain MRI must be performed at Screening for all participants. For participants with brain metastasis at Screening, brain MRI should then be performed Q9W until Week 52 of study intervention and Q12W thereafter until Week 104; after Week 104, imaging should be performed every Q24W, or sooner if clinically indicated. A brain MRI at EOT is required. Brain CT scan should only be used when MRI is contraindicated. The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden.

10.6.2.1.4 Section 1.3.4 Pembrolizumab + ATRA

Pembrolizumab + ATRA (SoA applicable to participants in this investigational arm)													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Administrative Procedures													
Concomitant medication review	X	X	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).
Randomization/ allocation	X												Participants may be randomized/allocated up to 24 hours before first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/allocation.
Access IXRS for pembrolizumab	X						X						Day 1 of every other cycle (eg, C1D1, C3D1, C5D1, etc.)
Pembrolizumab administration	X						X						Day 1 of every other cycle (eg, C1D1, C3D1, C5D1, etc.)
ATRA dispensed to participant	X			X			X						ATRA dispensed on D1 of each cycle for use during the following cycle.

Pembrolizumab + ATRA (SoA applicable to participants in this investigational arm)													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
ATRA administration	X						X						ATRA to be self-administered for 3 days of each q3w cycle. (See Section 10.6.2.17.1.1) Cycle 1 only: ATRA administration on Days 1,2, and 3. For all subsequent cycles, ATRA administration will on Days -1, 1, and 2 of each cycle.
Subsequent antineoplastic treatment									X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
DLT window	←-----→												The DLT window is defined as 1 cycle (3 weeks) from first dose of study intervention.
Survival status	←-----→												Participants may be contacted for survival status at any time during the course of this substudy.

Pembrolizumab + ATRA (SoA applicable to participants in this investigational arm)													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Efficacy/Immunogenicity Procedures													
Tumor assessment: chest, abdomen, and pelvis (CT/MRI) ^e	←-----→							X		X	X		On-study imaging to take place at Week 9 and every 9 weeks until Week 52; every 12 weeks until Week 104; and every 24 weeks thereafter. All imaging visits have a scheduling window of ±7 days. See Section 8.2.1 Tumor Imaging and Assessment of Disease. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of a stand-alone CT if it is of diagnostic quality per Site Imaging Manual.

Pembrolizumab + ATRA (SoA applicable to participants in this investigational arm)													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Digital photography	←-----→											Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.	
Safety Procedures													
AE monitoring	X	X	X	X	X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Directed physical examination	X		X	X		X	X	X	X				In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during this substudy, as clinically indicated.

Pembrolizumab + ATRA (SoA applicable to participants in this investigational arm)													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Vital signs (resting BP, heart rate, RR, and temp), and weight	X		X	X		X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 and Section 8.3.2 of this appendix for vital signs.
12-lead ECG	←-----→												As clinically indicated. Participants must be in the recumbent position for a period of 5 minutes before the ECG. See Section 8.3.3 for ECG.
Hematology and chemistry laboratory assessment	X		X	X		X	X	X	X				Procedures/assessments should be performed before all scheduled substudy visits. Every effort should be made to collect samples at the same time of day.
Urinalysis	←-----→												As clinically indicated.
PT/INR and aPTT/PTT	←-----→												As clinically indicated for participants taking anticoagulant therapy.

Pembrolizumab + ATRA (SoA applicable to participants in this investigational arm)													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
T3, FT4, TSH				X			X	X					Thyroid function tests will be performed at Cycle 2 and every other cycle thereafter (eg, C4, C6, etc.) and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1, retrospective review of thyroid function testing results is allowed when the results are not available before dosing.
Pregnancy test (WOCBP only)				X			X	X	X	X			To be assessed before all scheduled visits. A serum or urine pregnancy test will be performed as indicated, before every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.
ECOG performance status				X			X	X	X				To be assessed before dosing during all scheduled visits.

Pembrolizumab + ATRA (SoA applicable to participants in this investigational arm)													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	
Patient-reported Outcomes													
EORTC QLQ-30	X			X			X	X	X				Patient-reported outcomes will be assessed on Day 1 (before first dose of study intervention) of every cycle, at the Discontinuation Visit, and the 30-day Safety Follow-up Visit. If the EOT visit occurs 30 days from the last dose of study intervention, a 30-day required Safety Follow-up Visit is not required. ePROs do not need to be repeated. See additional details in Section 8.2.2.
EQ-5D-5L	X			X			X	X	X				
Biomarkers													



Pembrolizumab + ATRA (SoA applicable to participants in this investigational arm)													
Study Period	Treatment Cycle = 21 days							EOT ^c	Posttreatment				Notes All procedures and assessments are to be performed before administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.
									Safety ^c	Follow-up ^d		Survival	
Visit Timing/Cycle Number	1			2			Cycle 3 and Onwards ^b	At D/C	30 Days After Last Dose	Q12W	Q24W	Q12W	
Cycle Day	1	8	15	1	8	15	1						
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3		+7	±7	±7	±7	

CCI

ADA=antidrug antibody; AE=adverse event; aPTT=activated partial thromboplastin time; ATRA=all-trans retinoic acid; BICR=blinded independent central review; BP=blood pressure; C1=Cycle 1; C2=Cycle 2; C3=Cycle 3; C4=Cycle 4; C5=Cycle 5; C6=Cycle 6; CIV=central imaging vendor; CT=computed tomography; ctDNA=circulating tumor DNA; ctRNA=circulating tumor RNA; D1=Day 1; D8=Day 8; D15=Day 15; D/C=discontinue/discontinuing; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT=end of treatment; ePRO=electronic patient-reported outcome; EQ-5D-5L=European Quality of Life 5-dimension 5- level; FT4=free thyroxine; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRQoL=health-related quality of life; ICF=Informed Consent Form; INR=international normalized ratio; IXRS=interactive voice/web response system; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PE=physical examination; PET=positron emission tomography; PK=pharmacokinetics; PT=prothrombin time; PTT=partial thromboplastin time; q3w=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; qd=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; SIM=Site Imaging Manual; SoA=Schedule of Assessments; T3=triiodothyronine; TSH=thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP=women of childbearing potential.

- a This SoA is applicable to participants in Arm 3 pembrolizumab + ATRA.
- b Participants who attain an investigator-determined complete response (CR) and stop study intervention will have 30-day Safety Follow-up Visit and move to the follow-up visits per SoA.
- c If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up Visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up Visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.
- d For participants who D/C study intervention for reasons other than progressive disease, follow-up visits to monitor disease status continue until progressive disease or initiation of a new anticancer therapy. Participants who D/C study intervention due to progressive disease will proceed directly to Survival Follow-up.
- e A brain MRI must be performed at Screening for all participants. For participants with brain metastasis at Screening, brain MRI should then be performed Q9W until Week 52 of study intervention and Q12W thereafter until Week 104; after Week 104, imaging should be performed every Q24W, or sooner if clinically indicated. A brain MRI at EOT is required. Brain CT scan should only be used when MRI is contraindicated. The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden.

10.6.2.2 Section 2.4 Investigational Agent Pharmaceutical and Therapeutic Background

MK-7684 (anti-TIGIT)

MK-7684 is a humanized, antagonist IgG1 mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligand. This human IgG1 antibody is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with pembrolizumab (a humanized anti-PD-1 receptor antibody) to increase the benefit to patients with various tumor types including melanoma.

TIGIT is an immunomodulatory receptor expressed primarily on activated CD4+ and CD8+ T-cells, NK cells, and NK T-cells. Its structure reveals a single extracellular immunoglobulin domain, a transmembrane region, an ITT-like phosphorylation motif, and an ITIM.

TIGIT forms part of a comodulatory network that consists of a positive (CD226) and negative (TIGIT) immunomodulatory receptor on T-cells, and ligands (CD155 and CD112) expressed on tumor cells and antigen presenting cells [Levin, S. D., et al 2011]. Whereas CD226 is widely expressed on most immune cells, TIGIT is highly expressed on memory T-cells, Tregs, NK cells, and NK T-cells [Dardalhon, V., et al 2005] [Stanietsky, N., et al 2013]. CD155/PVR/Nect15/Tage4 and CD112/PVRL-2 are 2 nectin family members that are widely expressed both on cells of the hematopoietic system and on fibroblasts and endothelial cells. Functionally, these receptor ligands are involved in cell adhesion and motility. CD155 is reported to be overexpressed in several tumor types and has been found to be induced by Ras activation and genotoxic stress [Carlsten, M., et al 2007] [Hirota, T., et al 2005] [Masson, D., et al 2001].

Significant single-agent anti-TIGIT antitumor efficacy was observed in multiple preclinical tumor models, similar to the efficacy we observe with anti-PD-1 monotherapy. In addition, TIGIT is highly co-expressed with PD-1 on both CD4+ and CD8+ TILs including Tregs, in mouse and human tumors, and has been reported to be co-expressed with PD-1 and T-cell immunoglobulin and mucin domain containing-3 (Tim-3) on the TILs with the most exhausted phenotype [Chauvin, J. M., et al 2015] [Johnston, R. J., et al 2014]. Furthermore, enhanced antitumor efficacy is observed in preclinical models when an anti-TIGIT antibody is used with an anti-PD-1 antibody.

For additional information, refer to the MK-7684 IB.

MK-1308

MK-1308 is a humanized, antagonist mAb that binds CTLA-4 and blocks its interaction with both of its ligands, CD80 (B7.1) and CD86 (B7.2). This human IgG1 antibody is being developed for use in combination with pembrolizumab and other therapies to increase the antitumor efficacy in patients with various tumor indications, including melanoma.

CTLA-4 is a negative regulator of T-cell function and proliferation. It is found on the surface of activated T-cells and Tregs as a single-pass transmembrane protein belonging to the

immunoglobulin superfamily. CTLA-4 was identified as a second receptor for both CD80 and CD86 and shares some structural homology with the activating co-receptor CD28. Unlike CD28, which is expressed on naïve T-cells, the cell surface expression of CTLA-4 is both transient and tightly regulated. The opposing responses mediated by these 2 receptors are capable of coordinating the strength of the immune system's response.

As part of the adaptive immune response, T-cells are central to mounting a defense against tumor growth. Activation of T-cells is achieved via the dual engagement of both the T-cell receptor and CD28 receptor on the T-cell to mount a full immunogenic response. CD28 binds to either CD80 or CD86 molecules expressed on antigen presenting cells, leading to T-cell-specific expression and presentation of CTLA-4, which then competes with CD28 to bind either of these activating molecules, thereby dampening the activation signal for the T-cell, moving it to a more tolerogenic state. Therefore, blocking this immunomodulatory checkpoint, allowing T-cells to remain active, would allow the immune system to mount a more competent and durable antitumor response.

CTLA-4 suppression is thought to be primarily at sites of T-cell activation, eg, secondary lymph organs rather than within the tumor microenvironment. However, inhibition of CTLA-4 results in substantial increases of T-cell infiltrates within tumor tissues. This contrasts with the presumed inhibition of T-cell function via PD-1 engagement, which occurs within the tumor microenvironment between T-cells interacting with both antigen presenting cells and the tumor cells themselves. Differences in mechanism and expression of these receptors and their ligands suggest that these differential mechanisms of action may underlie the observed clinical benefit when utilized as combination therapy above their respective monotherapies.

For additional information, refer to the MK-1308 IB.

Lenvatinib

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGRs 1-3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. 2008] [Tammela, T. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR also play important roles for tumor angiogenesis [Cross, M. J. 2001] [Lieu, C., et al 2011] [Limaverde-Sousa, G., et al 2014].

Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFR α , KIT, and RET. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis.

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of HUVEC with IC₅₀ values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that

lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

In summary, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in HUVEC models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer drugs.

ATRA (VESANOID®)

ATRA is a vitamin A derivative that binds the retinoic acid receptor on MDSCs and differentiates immature monocytes into more mature dendritic cells [Nefedova, Y., et al 2007]. VESANOID is a standard treatment currently approved for patients with APL.

VESANOID is an FDA-approved commercially available retinoid that induces maturation of APL cells in culture. It is not approved in combination with pembrolizumab or for the treatment of patients with melanoma. It is available in a 10 mg soft gelatin capsule for oral administration. The recommended dose (for APL) is 45 mg/m²/day administered as 2 evenly divided doses until complete remission is documented.

For additional information, refer to the VESANOID prescribing information.

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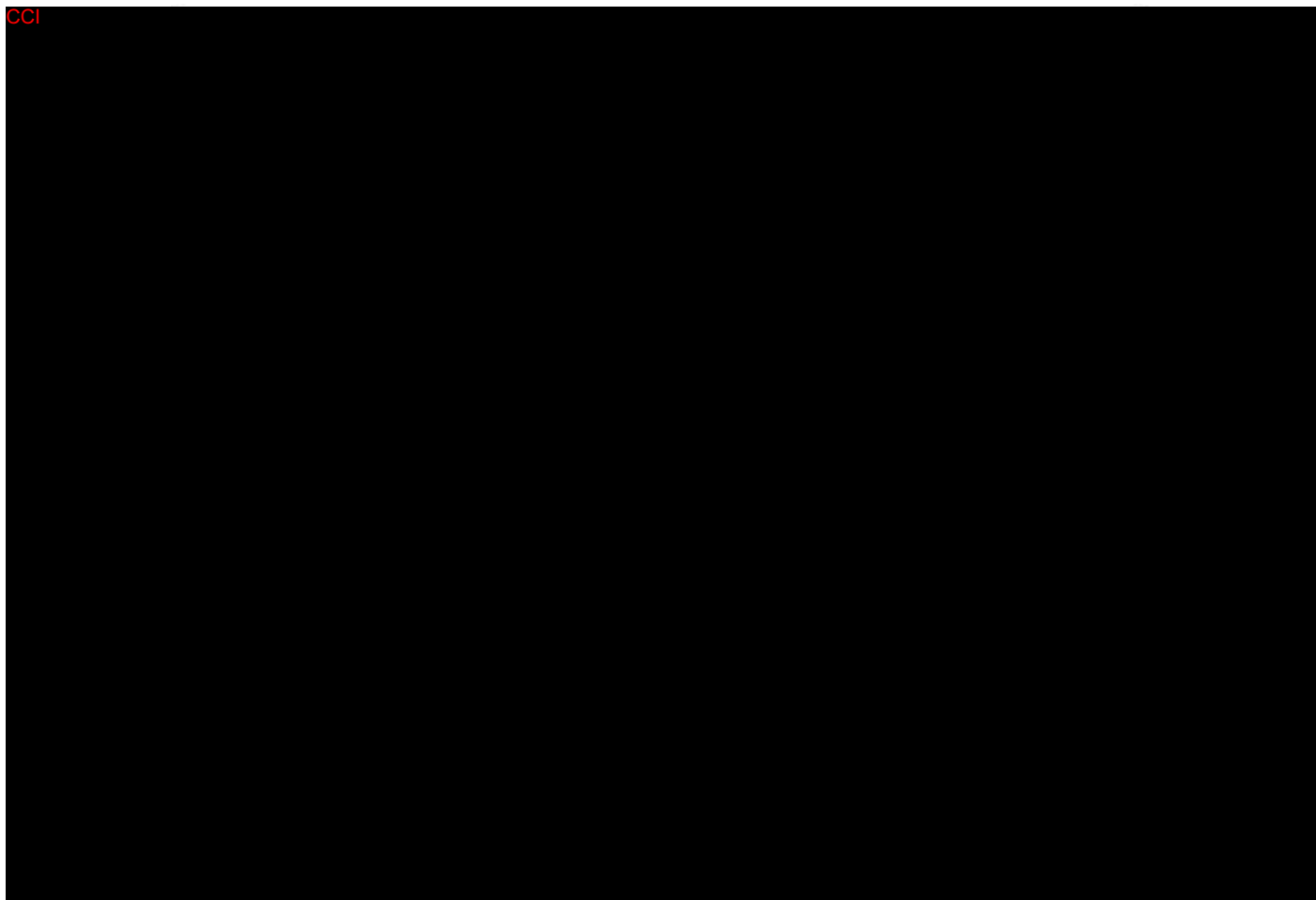
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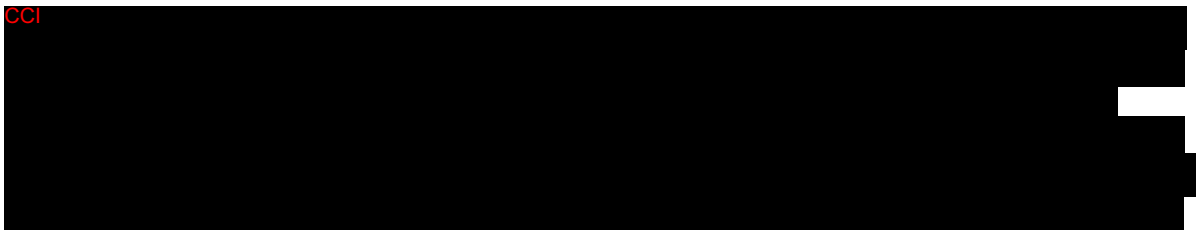
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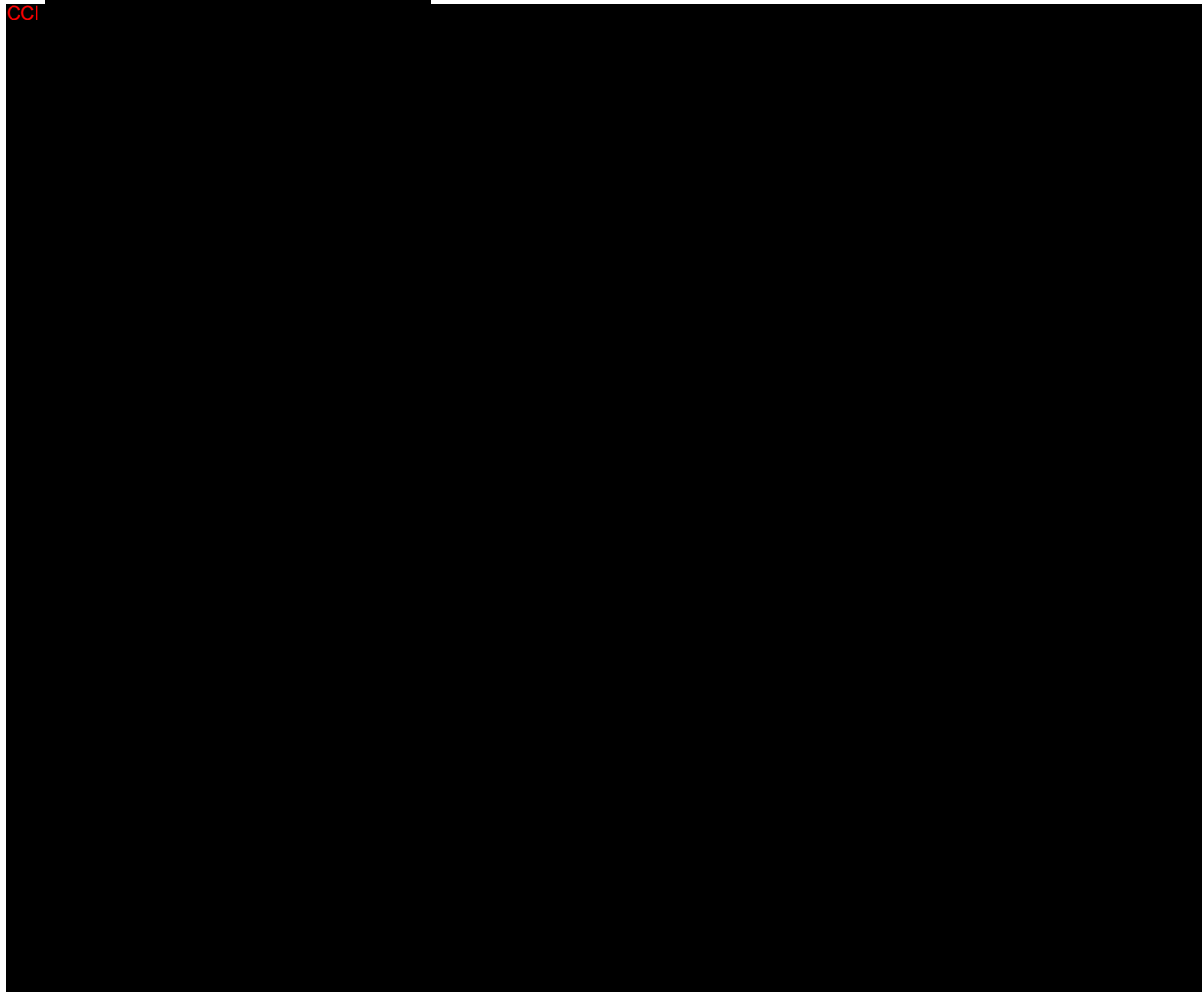
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10.6.2.2.2 Section 2.4.2 Ongoing Clinical Studies

MK-7684 (anti-TIGIT)

Protocol 7684-001 is the first-in-human clinical study of MK-7684.

For additional information, refer to the MK-7684 IB. As accumulating safety data from human participants are available for MK-7684, the reference safety information of expected related AE terms (ie, AR) using current MedDRA Preferred terms will be updated in the IB.

MK-1308

Protocol 1308-001 is the first-in-human clinical study of MK-1308.

For additional information, refer to the MK-1308 IB. As accumulating safety data from human participants are available for MK-1308, the reference safety information of expected related AE terms (ie, AR) using current MedDRA Preferred terms will be updated in the IB.

Lenvatinib

Refer to the lenvatinib IB for clinical study data.

ATRA

Refer to the VESANOID prescribing information and Section 2.5 of the Appendix for clinical study data.

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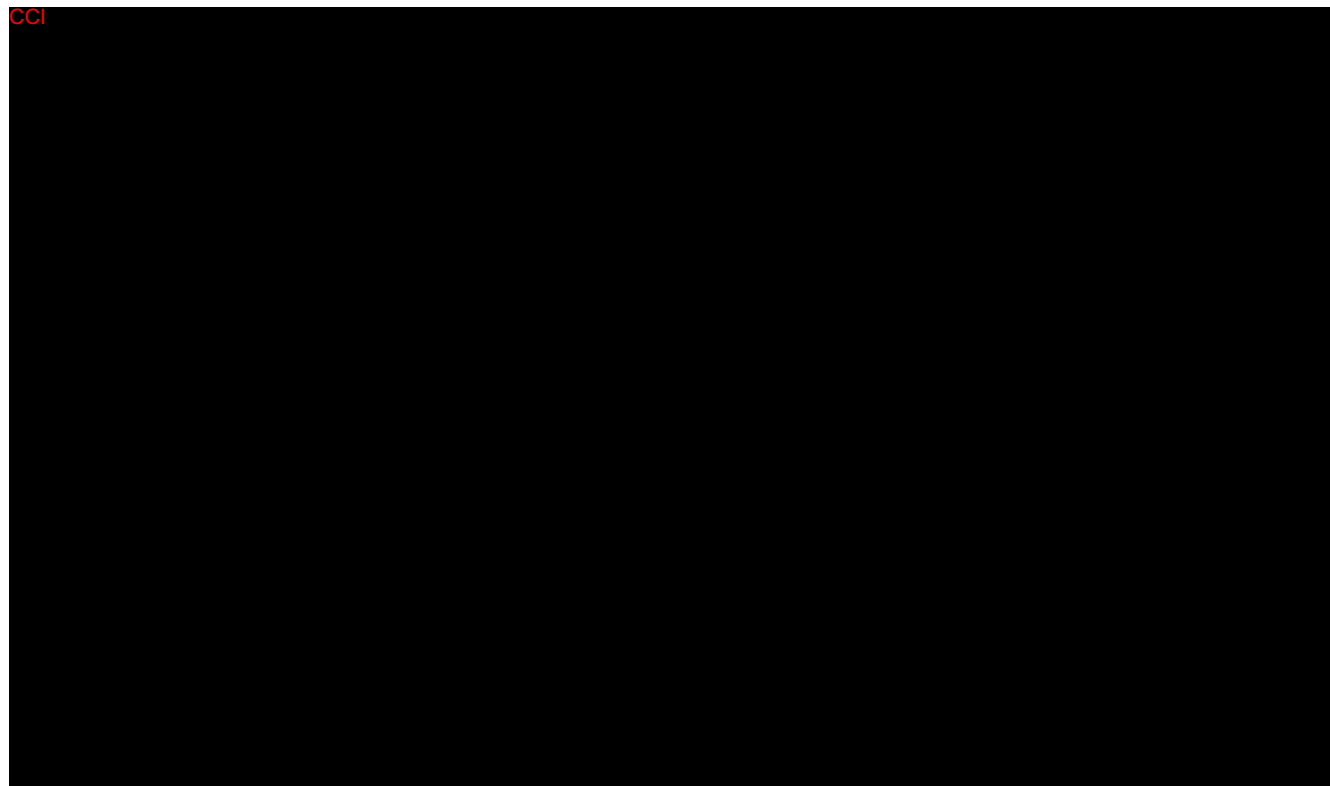
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10.6.2.4 Section 2.6 Clinical Data on the Investigational Agents With or Without Pembrolizumab

Pembrolizumab with MK-7684 (anti-TIGIT)

MK-7684-001 is a Phase 1, open-label, multi-arm, multicenter dose-finding clinical study (NCT02964013). During dose escalation, MK-7684 was evaluated as monotherapy (n = 34) and in combination with pembrolizumab (n = 34) in 68 participants with advanced solid tumors who failed standard treatment options. Thirteen participants who progressed on the monotherapy arm crossed over to the combination arm. MK-7684 (dose ranges: 2.1, 7, 21, 70, 210, and 700 mg) and pembrolizumab (200 mg fixed dose) were administered q3w for up to 35 cycles or until progression, intolerable toxicity, or investigator or participant decision. Primary study objectives included evaluation of safety and tolerability, PK, and ORR as determined by RECIST 1.1. CCI

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Pembrolizumab with MK-1308

An ongoing, multicenter, multi-arm, open-label Phase 1b study (MK-1308-001) is evaluating MK-1308 in combination with pembrolizumab in participants with solid tumors (NCT03179436). In dose escalation, MK-1308 was given at either 25 mg or 75 mg (Cohorts 1 and 2) IV q3w as monotherapy × 1 cycle, in combination with pembrolizumab 200 mg q3w × 4 cycles, followed by pembrolizumab monotherapy. In Dose Confirmation, participants with 1L advanced NSCLC were treated with MK-1308 at 25 mg q3w (Arm A), 25 mg q6w (Arm B), or 75 mg q6w (Arm C), in combination with pembrolizumab 200 mg q3w. Response was assessed Q9W.

This first-in-human study of MK-1308 was designed to assess the safety, tolerability, PK, and pharmacodynamics of escalating doses of MK-1308 when used in combination with pembrolizumab in participants with advanced/metastatic solid tumors refractory to conventional therapy, 1L treatment-naïve NSCLC, and 2L SCLC. It is reasonable to expect the PK of MK-1308 to be consistent with that of other humanized mAbs that typically have a low clearance and a limited volume of distribution. Using a population PK model of ipilimumab, distribution of exposures from the 25 mg MK-1308 fixed dose overlapped considerably with those obtained with the 0.3 mg/kg weight-based ipilimumab dose, and exposures from the 75 mg MK-1308 fixed dose overlapped considerably with those obtained with the 1.0 mg/kg weight-based ipilimumab dose [Feng, Y., et al 2014]. Similar to pembrolizumab, a fixed-dose regimen of MK-1308 is expected to reduce complexity in the logistical chain at treatment facilities and to reduce waste. The goal in introducing the lower doses of 25 mg MK-1308 at the schedule of either q3w or q6w was to determine if a similar response rate could be achieved at lower doses, which would be expected to result in a reduction in immune-related toxicities from CTLA-4 antagonism. The goal in evaluating the 75 mg MK-1308 dose at the q6w interval was to achieve the expected response rates with similar acceptable toxicity and discontinuation rates based on the Phase 1 CheckMate-012 results in the NSCLC population [Hellmann, M. D., et al 2016]. Details regarding specific benefits and risks for participants participating in this clinical study may be found in the IB and informed consent documents.

Participants with advanced melanoma that is refractory to PD-1/L1 are planned to be enrolled in this study in the Efficacy Expansion Phase based on the following evidence: (1) improved response rates after ipilimumab/nivolumab in the CheckMate 067 study; (2) improved response rates after treatment with ipilimumab/pembrolizumab in the KEYNOTE-029 study; and (3) the results from a MSD single-institution collaborative study in a similar melanoma population [Wolchok, J. D., et al 2017] [Long, G. V., et al 2017] [Olsonm, D., et al 2018].

An IA of MK-1308 safety, antitumor activity, PK, and pharmacodynamic biomarker data was performed for the Dose Escalation and Dose Confirmation phases of the study based on a 07-NOV-2018 database lock. The ORR by BICR with confirmation for MK-1308 25 mg administered q6w in the advanced 1L NSCLC population (Arm B) was similar to the ORR for the 75 mg dose level given q6w (33% versus 22%, respectively). The target rate for DLT was not reached in any of Cohorts 1, 2, or 3; however, a higher toxicity rate correlated with a higher MK-1308 dose among several different AE characteristics, including drug-related AEs, Grade 3 to 5 AEs, SAEs, and AEs leading to treatment discontinuation or modification.

The Grade 3 to 5 AE rate was 29% in Cohort 1, 71% in Cohort 2, and 100% in Cohort 3. In the Dose Confirmation Phase, a lower MK-1308 dose and a longer treatment interval had a more favorable toxicity profile (45% in Arm B, 48% in Arm A, 53% in Arm C, and 86% in Arm E [MK-1308 75 mg in combination with pembrolizumab 200 mg q3w]). Time to first Grade 3 to 5 AE was more rapid at a higher MK-1308 dose and with more frequent dosing (7 months in Arm B, 5.2 months in Arm A, 5.6 months in Arm C, and 1.1 month in Arm E). The most common AEs were fatigue (24.9%), pruritus (24.4%), rash (23.5%), decreased appetite (22.5%), AST increased (19.2%), ALT increased (17.4%), diarrhea (16.4%), and hypothyroidism (16%). In totality, the efficacy, safety, and PK data led to the selection of 25 mg given q6w as the RP2D for MK-1308 for use in combination with pembrolizumab.

Pembrolizumab with Lenvatinib

E7080-A001-111/KEYNOTE-146 is an ongoing multicohort Phase 2 study to assess the efficacy and safety of lenvatinib in combination with pembrolizumab in 6 types of biomarker-unselected metastatic solid tumors, including melanoma (excluding uveal melanoma), that have progressed after treatment with approved therapies or for which there are no standard effective therapies available. The study is ongoing but is no longer enrolling melanoma patients.

Eligible patients are aged 18 years or older and have histologically confirmed nonuveal melanoma, 0 to 2 prior systemic anticancer regimens, and an ECOG score of 0 or 1. The primary endpoint is ORR at Week 24 based on iRECIST, as determined by investigator-read tumor assessments performed at baseline, q6w until Week 24, and then Q9W thereafter. Secondary endpoints include ORR, DOR, PFS, OS, and safety and tolerability of the combination. All participants received lenvatinib 20 mg daily in combination with 200 mg pembrolizumab IV q3w. At data cutoff (01-MAR-2018), 21 metastatic melanoma patients were enrolled, and 38% of participants had 1 or more prior anticancer therapy.

For all enrolled participants (N = 21), the ORR at Week 24 was 47.6% (95% CI: 25.7, 70.2) using iRECIST by investigator review. Of the 10 confirmed responses, 9 (42.9%) were PR, and 1 (4.8%) was CR. Stable disease was observed in 7 (33.3%) participants, and 3 (14.3%) experienced progressive disease. One participant had an unknown response. Median duration of objective response was 12.5 months (95% CI, 2.7 months, NE). Median PFS observed was 7.6 months (95% CI: 2.6 months, 15.8 months).

All participants experienced ≥ 1 treatment-related AE. There were no fatal treatment-related AEs. The most common any-grade treatment-related AEs were fatigue (52%), decreased appetite (48%), diarrhea (48%), hypertension (48%), dysphonia (43%), and nausea (43%). Dose reduction and interruption due to treatment-related AEs occurred in 13 (62%) and 10 (47.6%) participants, respectively. The safety profile of lenvatinib in combination with pembrolizumab appears manageable in patients with malignant melanoma and other tumor types and is consistent with each agent's safety profile when administered as monotherapy.

Pembrolizumab with ATRA

NCT03200847 is a single-arm, single-institution, Phase 1/2 clinical study which has enrolled 24 patients diagnosed with Stage IV melanoma. Eligible patients were ≥ 18 and had not been previously treated with anti-PD-1 therapy. Treatment consisted of pembrolizumab 200mg q3w plus the supplemental treatment of ATRA 150 mg/m² orally for 3 days surrounding each of the first 4 pembrolizumab infusions, with patients continuing pembrolizumab for up to 2 years until confirmed disease progression or unacceptable toxicity. The primary endpoints were to establish the MTD and RP2D. Secondary endpoints were safety, reduction in circulating MDSCs, assessments of antitumor activity.

At data cut off (February 2021) 22 patients were evaluable for tumor response. Median follow-up was 1.0 years (0.3-2 years). The ORR was 60% and DCR was 83%. Six-month PFS rate was 62%. Excluding patients diagnosed with uveal melanoma (n = 2) the ORR was 72%, DCR was 86%, and the six-month PFS rate was 68%. Paired analysis showed sustained decreases in absolute numbers ($p=0.002$) and percentage ($p=0.007$) of circulating MDSCs (CD3⁺CD19⁻CD56⁻CD11b⁺CD33⁺HLA-DR^{-low}) 4 to 6 weeks after stopping ATRA.

In general, the combination of pembrolizumab and ATRA was well tolerated. The most common treatment-related AEs were Grade 1 or 2, including headache (22 pts, 92%), fatigue (18 pts, 75%), rash (16 pts, 66%), and nausea (8 pts, 33%), most of which corresponded with the 3-day course of ATRA treatment. Ten patients had Grade 3 or higher AEs with most being common ICI-related AEs.

This study is ongoing [McCarter, M., et al 2021].

10.6.2.5 Section 4.1 Overall Design of the Substudy

10.6.2.5.1 Section 4.1.1 Investigational Treatment Arms

Safety Lead-In Phase

Participants will receive treatment with a pembrolizumab-based/non-pembrolizumab-based combination:

- Investigational Treatment Arm 1: Participants will receive pembrolizumab (at a fixed dose of 200 mg q3w) in combination with MK-7684 (at a fixed dose of 200 mg q3w) and MK-1308 (at a fixed dose of 25 mg q6w).
- Investigational Treatment Arm 2: Participants will receive pembrolizumab (at a fixed dose of 400 mg q6w) in combination with MK-1308 (at a fixed dose of 25 mg q6w), and lenvatinib (at a fixed dose of 20 mg qd PO).
- Investigational Treatment Arm 3: There will be no Safety Lead-in Phase.

The Common Terminology Criteria for Adverse Events, version 5, must be used to grade the severity of adverse events.

Investigational Treatment Arm 1: There is only 1 predetermined dose level of pembrolizumab in combination with MK-7684 and MK-1308 that will be explored (Dose Level 0).

	Dose Level 0
Pembrolizumab	200 mg
MK-7684	200 mg
MK-1308	25 mg

Initially, 3 DLT evaluable participants will be enrolled in Dose Level 0. More than 3 to 6 participants may be enrolled to Dose Level 0 if needed to replace participants who are not evaluable for DLT or to ensure a thorough evaluation of the dose level during the Safety Lead-In Phase as per Section 5.5. ^{CCI}

^{CCI} Patients who experience a DLT will be allowed to remain on the substudy if they meet the following criteria: (1) the investigator believes it is appropriate for participant to remain on the substudy, and (2) the event has resolved and no longer meets the definition of DLT.

^{CCI}

As participants become evaluable for DLT assessment, the number of participants who are evaluable for DLT versus the number of participants who developed a DLT will be continuously assessed as shown in [Table 5](#).

Participants may not have any dose modifications of MK-7684, MK-1308 or pembrolizumab in this investigational treatment arm, as described in [Table 3](#). If toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from the agents.

The investigator may attribute each toxicity event to MK-7684 alone, to MK-1308 alone, to pembrolizumab alone, or to the combination, and follow the dose delay and restart criteria according to [Table 3](#).

Holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study interventions. For example, in the combination arm, if MK-7684 or MK-1308 is held due to an adverse event attributed to that drug, pembrolizumab may continue to be administered. Appropriate documentation is required regarding which drug the investigator is attributing to the adverse event. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, then both drugs should be held according to recommended dose modifications. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

If toxicity does not resolve to Grade 0 to 1 within 12 weeks after last treatment, MK-7684 and/or MK-1308 and/or pembrolizumab should be discontinued after consultation with the Sponsor.

With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the study only if asymptomatic and controlled.

After any Grade 4 drug-related AE, participants should not restart study intervention without consultation with the Sponsor (toxicity must have resolved to Grade 0 to 1 or baseline before restarting).

Investigational Treatment Arm 2: There are 3 predetermined dose levels of pembrolizumab in combination with MK-1308 and lenvatinib that may be explored (Dose Level 0, Dose Level -1 and Dose Level -2).

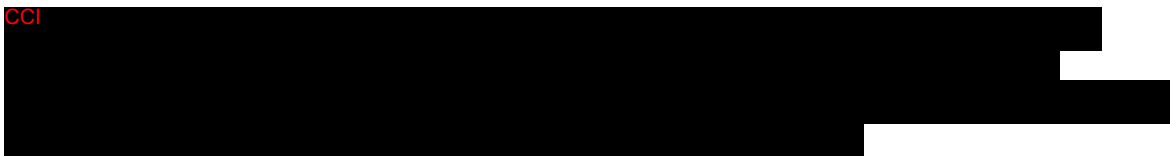
	Dose Level 0	Dose Level -1	Dose Level -2
Pembrolizumab	400 mg	400 mg	400 mg
MK-1308	25 mg	25 mg	25 mg
Lenvatinib	20 mg	14 mg	10 mg

Initially, 3 DLT evaluable participants will be enrolled in Dose Level 0. More than 3 to 6 participants may be enrolled to Dose Level 0 if needed to replace participants who are not evaluable for DLT or to ensure a thorough evaluation of the dose level during the Safety Lead-In Phase as per Section 5.5. ^{CCI}

Patients who experience a DLT will be allowed to remain on the substudy if they meet the following criteria: (1) the investigator believes it is appropriate for participant to remain on the substudy, and (2) the event has resolved and no longer meets the definition of DLT.

Dose recommendations for the next evaluable participants will depend on the observed number of DLTs in the first 3 DLT evaluable participants and ^{CCI} In

the event Dose Level 0 is not tolerable, lower dose levels may be selected. As participants become evaluable for DLT assessment, the number of participants who are evaluable for DLT versus the number of participants who developed a DLT will be continuously assessed as shown in [Table 5](#).



The investigator may attribute each toxicity event to lenvatinib alone, to MK-1308 alone, to pembrolizumab alone, or to the combination, and follow the dose delay and restart criteria according to [Table 3](#) for MK-1308 and pembrolizumab and [Table 14](#) for lenvatinib. Participants may not have any dose modifications of MK-1308 or pembrolizumab in this investigational treatment arm, as described in [Table 3](#). If toxicity attributed to MK-1308 or pembrolizumab does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from MK-1308 or pembrolizumab. Participants may have dose modifications of lenvatinib in this investigational treatment arm, as described in [Table 14](#). If toxicity attributed to lenvatinib does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from lenvatinib.

Holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study interventions. For example, in the combination arm, if MK-1308 or pembrolizumab is held due to an adverse event attributed to that drug, lenvatinib may continue to be administered. Appropriate documentation is required regarding which drug the investigator is attributing to the adverse event. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, then both drugs should be held according to recommended dose modifications. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

If toxicity does not resolve to Grade 0 to 1 within 12 weeks after last treatment, MK-1308 and/or pembrolizumab and/or lenvatinib should be discontinued after consultation with the Sponsor.

With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the study only if asymptomatic and controlled.

After any Grade 4 drug-related AE, participants should not restart study intervention without consultation with the Sponsor. (Toxicity must have resolved to Grade 0 to 1 or baseline before restarting).

10.6.2.6 Section 4.3 Justification for Dose

10.6.2.6.1

CCI

CCI

[REDACTED]

[REDACTED]

[REDACTED]

CCI

[REDACTED]

CCI

[REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10.6.2.7 Section 5.1 Inclusion Criteria Specific to the Investigational Agents Being Evaluated

These Inclusion Criteria are applicable to ALL PARTICIPANTS being screened to any open arm within this substudy.

Investigational-agent-specific inclusion criteria

Male Participants

15. Male participants are eligible to participate if they agree to the following during treatment with and for at least 7 days after the last dose of lenvatinib or ATRA:

- Be abstinent from heterosexual intercourse 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 unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:
 - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Note: For male participants who only receive pembrolizumab, MK-1308, MK-7684, or a combination of the aforementioned drugs, no contraception measures are needed.

Female Participants

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

- 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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of pembrolizumab, MK-1308, MK-7684, or 30 days after the last dose of lenvatinib or ATRA, whichever occurs last. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- WOCBP who choose to remain abstinent from heterosexual intercourse should do so during the entire period of risk associated with the study intervention.
 - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
 - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
 - Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.
- 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.

Medical History and Laboratory Values

17. Have adequately controlled BP with or without antihypertensive medications, defined as BP $\leq$ 150/90 mm Hg with no change in antihypertensive medications within 1 week before randomization.

Type of Participant and Disease Characteristics

18. Participants in France only: Prior therapy with systemic anti-TIGIT therapy will not be allowed.

10.6.2.8 Section 5.2 Exclusion Criteria Specific to the Investigational Agents Being Evaluated

These Exclusion Criteria are applicable to ALL PARTICIPANTS being screened to any open arm within this substudy.

Investigational-agent-specific exclusion criteria:

21. Has a pre-existing Grade $\geq$ 3 gastrointestinal or nongastrointestinal fistula.
22. Has radiographic evidence of encasement of invasion of a major blood vessel, or of intratumoral cavitation.
Note: the degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.
23. Has clinically significant hemoptysis or tumor bleeding within 2 weeks before the first dose of study intervention.

24. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.
Note: Medically controlled arrhythmia would be permitted.
25. Has urine protein ≥ 1 g/24-hour.
Note: Participants having $>1+$ proteinuria on urine dipstick testing/urinalysis will undergo 24-hour urine collection for quantitative assessment of proteinuria.
26. Has prolongation of QTc interval (calculated using Fridericia's formula) to >480 msec.
27. Has LVEF below the institutional normal range as determined by MUGA or echocardiogram.
28. Has presence of gastrointestinal condition including malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.
29. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.

10.6.2.9 Section 5.3 Lifestyle Considerations

ATRA

The following precautions appear in the VESANOID package insert:

1. The ability to drive or operate machinery might be impaired in patients treated with VESANOID, particularly if they are experiencing dizziness or severe headache.
2. As with other retinoids, ATRA must not be administered in combination with vitamin A because symptoms of hypervitaminosis A could be aggravated.
3. Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with ATRA and anti-fibrinolytic agents. Therefore, caution should be exercised when administering ATRA concomitantly with these agents.

10.6.2.9.1 Section 5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

MK-7684 (anti-TIGIT)

None.

MK-1308

None.

Lenvatinib

None.

ATRA

None.

10.6.2.9.2 Section 5.3.4 Investigational Agent Contraception, Pregnancy, and Use in Nursing Women

MK-7684, MK-1308, and ATRA may have adverse effects on a fetus in utero. Contraception requirements for this study are outlined in Appendix 5.

Lenvatinib

Lenvatinib may have adverse effects on a fetus in utero. Contraception requirements for this study are outlined in Appendix 5.

Lenvatinib may impair fertility in men and women of reproductive potential. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during treatment with lenvatinib and for at least 30 days after the last dose.

ATRA

ATRA may have adverse effects on a fetus in utero. Contraception requirements for this study are outlined in Appendix 5.

Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during treatment with ATRA and for at least 30 days after the last dose.

10.6.2.10 Section 6.1 Study Intervention(s) Administered

Study interventions will be administered on an outpatient basis. The investigational agents to be used in this substudy protocol are outlined in [Table 13](#).

Table 13 Study Intervention

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strengths	Dosage Levels	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Arm 1 ^a	Experimental	MK-7684 (anti-TIGIT)	Drug	Solution for Infusion	50 mg/mL	200 mg	IV Infusion	q3w	Experimental	IMP	Central
Arm 1 ^a and Arm 2 ^b	Experimental	MK-1308	Drug	Solution for Infusion	50 mg/mL	25 mg	IV Infusion	q6w	Experimental	IMP	Central
Arm 2 ^b	Experimental	Lenvatinib	Drug	Capsule	10 mg 4 mg ^c	20 mg	Oral	Once daily	Experimental	IMP	Central
Arm 3 ^b	Experimental	ATRA	Drug	Capsule	10 mg	75 mg/m ²	Oral	Twice per day for 3 days q3w	Experimental	IMP	Central or Local

ATRA=all-trans retinoic acid; IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product; q3w=every 3 weeks, q6w=every 6 weeks.

^a For Arm 1, pembrolizumab will be administered at a dose of 200 mg q3w.

^b For Arm 2 and Arm 3, pembrolizumab will be administered at a dose of 400 mg q6w.

^c 4 mg capsules provided for successive dose reduction of lenvatinib, if needed, as described in Section 6.6.2 of this appendix.

Note: Definition of IMP and NIMP is based on guidance issued by the European Commission. Regional and/or country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

10.6.2.11 Section 6.2 Preparation/Handling/Storage/Accountability

10.6.2.11.1 Section 6.2.1 Dose Preparation: MK-7684, MK-1308, Lenvatinib, and ATRA

Details on preparation and administration of MK-7684 and MK-1308 are provided in the Pharmacy Manual.

Lenvatinib is a capsule for oral administration and does not require preparation. If a dose of lenvatinib is missed and cannot be taken within 12 hours from the scheduled administration, the participant should skip this dose and take the next dose at the scheduled time the next day. See Pharmacy Manual for additional information.

ATRA is a capsule for oral administration and does not require preparation. See the Pharmacy Manual for additional details.

For additional information, refer to the MK-7684, MK-1308, and lenvatinib IBs.

10.6.2.11.2 Section 6.2.2 Handling, Storage, and Accountability

MK-7684 (anti-TIGIT)

Stability studies of MK-7684 solution for infusion are in progress to confirm that, throughout the duration of the clinical studies, clinical supplies remain within specifications. The proposed shelf-life for the solution for infusion is based on the available stability data when stored according to conditions specified in the clinical supplies labeling. As additional stability data become available, the shelf-life may be extended. For each individual substudy, clinical supplies are to be stored in accordance with specific instructions on the label.

Refer to Section 6.2.2 of this substudy protocol for accountability instructions. For additional information, refer to the MK-7684 IB and the Pharmacy Manual.

MK-1308

Stability studies of MK-1308 are in progress to confirm that, throughout the duration of the clinical studies, clinical supplies remain within specifications. The proposed shelf-life for the solution for infusion is based on the available stability data when stored according to conditions specified in the clinical supplies labeling. As additional stability data become available, the shelf-life may be extended. For each individual substudy, clinical supplies are to be stored in accordance with specific instructions on the label.

Refer to Section 6.2.2 of this substudy protocol for accountability instructions. For additional information, refer to the MK-1308 IB and the Pharmacy Manual.

Lenvatinib

Lenvatinib will be provided centrally. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number,

manufacturer, and expiry date for any locally purchased product per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 6.2.2 of this substudy protocol for accountability instructions. For additional information, refer to the lenvatinib IB and the Pharmacy Manual.

ATRA

ATRA will be provided either locally or centrally (by country). Refer to Section 6.2.2 of this substudy protocol for accountability instructions. For additional information, refer to the ATRA prescribing information.

10.6.2.12 Section 6.3 Measures to Minimize Bias: Randomization and Blinding

10.6.2.12.1 Section 6.3.1 Intervention Assignment

Participants eligible for this substudy protocol will be randomly assigned to open investigational treatment arms centrally using an IRT system. For additional details on study intervention assignment, refer to Section 6.3.1 of this substudy protocol.

10.6.2.13 Section 6.4 Study Intervention Compliance

MK-7684 (anti-TIGIT)

Refer to Section 6.4 of the main protocol for instructions that apply to study intervention compliance when study intervention is infused.

MK-1308

Refer to Section 6.4 of the main protocol for instructions that apply to study intervention compliance when study intervention is infused.

Lenvatinib

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

ATRA

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

10.6.2.14 Section 6.5 Concomitant Therapy

10.6.2.14.1 Section 6.5.2 Prohibited Concomitant Medications

MK-7684 (anti-TIGIT)

None.

MK-1308

None.

Lenvatinib

None.

ATRA

None.

10.6.2.14.2 Section 6.5.3 Rescue Medications and Supportive Care

MK-7684 (anti-TIGIT)

None. Refer to Section 6.5.3 of this substudy protocol for instructions that apply to immunomodulatory agents.

MK-1308

None. Refer to Section 6.5.3 of this substudy protocol for instructions that apply to immunomodulatory agents.

Lenvatinib

For participants receiving lenvatinib, suggested supportive care measures for the management of AEs are outlined in [Table 14](#) in Section 6.6.2 of this appendix.

ATRA

There has been no experience with acute overdosage in humans. Overdosage with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness, and ataxia. These symptoms have quickly resolved without apparent residual effects. Supportive symptomatic care can be provided at the investigator's discretion. Dose modification guidelines for ATRA-related AEs are provided in [Table 15](#).

10.6.2.14.3 Section 6.5.5 Drug Interactions

MK-7684 (anti-TIGIT)

Not applicable.

MK-1308

Not applicable.

Lenvatinib

There are no DDI-related concomitant medication prohibitions or restrictions.

Lenvatinib is not expected to clinically alter exposure to CYP3A4/ Pgp substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and Pgp substrate). Clinical studies also showed that co-administration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp are not of clinical concern.

No drug interaction is expected between pembrolizumab and lenvatinib because of divergent metabolic pathways. Pembrolizumab is a monoclonal antibody and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (lenvatinib IB).

ATRA

There are no drug-drug interaction-related concomitant medication prohibitions or restrictions. No DDI are expected between pembrolizumab and ATRA because ATRA is a small, non-protein molecule.

As ATRA is metabolized by the hepatic P450 system, there is a potential for alteration of pharmacokinetics parameters in patients administered concomitant medications that are also inducers or inhibitors of this system. Medications that generally induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital, and pentobarbital. Medications that generally inhibit hepatic P450 enzymes include ketoconazole, cimetidine, erythromycin, verapamil, diltiazem, and cyclosporine. To date there are no data to suggest that co-use with these medications increases or decreases either efficacy or toxicity of ATRA.

10.6.2.15 Section 6.6 Dose Modification (Escalation/Titration/Other)

10.6.2.15.1 Section 6.6.2 Dose Modification for Investigational Agent Intervention

Dose Modification and Toxicity Management for Adverse Events Associated With Pembrolizumab and/or MK-7684 and/or MK-1308 and/or Lenvatinib and/or ATRA

MK-7684 (anti-TIGIT)

Adverse events associated with MK-7684 exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of study intervention and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications.

Dose modification instructions provided for pembrolizumab in Section 6.6.1 of this protocol should be followed for MK-7684 as well as they generally apply to immunomodulatory agents.

MK-1308

Adverse events associated with MK-1308 exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of study intervention and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications.

Dose modification instructions provided for pembrolizumab in Section 6.6.1 of this substudy protocol should be followed for MK-1308 as well, as they generally apply to immunomodulatory agents.

Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-related toxicity will be in accordance with the dose modification guidelines described in [Table 14](#). An interruption of study intervention with lenvatinib for more than 28 days will require Sponsor approval before treatment can be resumed.

Adverse events will be graded using NCI CTCAE version 5.0. Investigators will decide the probability of the event being related to 1 or a combination of drugs as to whether dose modification of 1 or the combination of drugs is required.

The starting dose of lenvatinib is 20 mg/day. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the Sponsor. Once the lenvatinib dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Refer to the subsections below for management of hypertension, proteinuria, diarrhea, hepatotoxicity, thromboembolic events, PRES/RPLS, hypocalcemia, hemorrhage, and gastrointestinal perforation or fistula formation, osteonecrosis of jaw as appropriate, before consulting the dose modification table ([Table 14](#)). For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Appendix 6, Section 10.6.2.15.2.

Table 14 Dose Modification Guidelines for Lenvatinib-Related Adverse Events

Treatment-Related Toxicity ^{a,b}	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2^{c,d} or Grade 3^{e,g}		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4^f: Discontinue Study Intervention		

AE=adverse event; BMI=body mass index; CTCAE=Common Terminology Criteria for Adverse Events.

Note: For grading see CTCAE version 5.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

- a An interruption of study intervention with lenvatinib for more than 28 days will require Sponsor approval before study intervention can be resumed.
- b Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea before any lenvatinib interruption or dose reduction.
- c Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.
- d Obese participants (BMI ≥ 30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they reach at least a BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.
- e For asymptomatic laboratory abnormalities, such as Grade ≥ 3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.
- f Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
- g For Grade 3 thromboembolic event, permanently discontinue lenvatinib.

Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP of $\leq 150/90$ mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week

before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 1.3.1 and Section 1.3.3 of this appendix). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the participant's initial BP measurement is elevated (ie, systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the participant's clinical circumstances and follow standard medical practice. For previously normotensive participants, appropriate antihypertensive therapy should be started when systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a participant is at imminent risk to develop a hypertensive crisis or has uncontrolled hypertension (eg, BP $\geq 160/100$ mm Hg) with significant risk factors for severe complications, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the participant has been on the same antihypertensive medications for at least 48 hours and their BP is controlled, lenvatinib should be resumed as described below.

Participants who have had systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg occurs, the participant must resume the Day 15 evaluation until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 2 consecutive treatment cycles. A diary may be provided to the participant to capture the BP evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg confirmed on 2 BP assessments at least 30 minutes:

1. Continue study intervention and institute antihypertensive therapy for participants not already receiving this.

2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study intervention can be continued without dose modification.
3. If systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP is ≤ 150 mm Hg and diastolic BP is ≤ 95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
 - If systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP is ≤ 150 mm Hg and diastolic BP is ≤ 95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
 - If systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP is ≤ 150 mm Hg and diastolic BP is ≤ 95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
 - Additional dose reduction should be discussed with the Sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

1. Institute appropriate medical management
2. Discontinue study intervention

Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA (Section 1.3.3 of this appendix). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing per the SoA (Section 1.3.1 and Section 1.3.3 of this appendix)

2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot UPCR test) is required in the following situations:
 - The first (initial) occurrence of $\geq 2+$ proteinuria on urine dipstick while on lenvatinib
 - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
 - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is $\geq 2+$.
3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥ 2.4 .

Grading of Proteinuria

- Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained. If the participant had 4+ proteinuria by dipstick, a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to [Table 14](#).

Monitoring

- Urine dipstick testing for participants with proteinuria $\geq 2+$ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.
- Proteinuria monitoring can be performed at the local laboratory or investigator site but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

Management of Diarrhea

An antidiarrheal agent should be recommended to the participant at the start of study intervention, and participants should be instructed and educated to initiate antidiarrheal treatment at the first onset of soft bowel movements. The choice of antidiarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in [Table 14](#) should be followed.

Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the SoA (Section 1.3.1 and Section 1.3.3 of this appendix) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in [Table 14](#) should be

followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, the study intervention must be discontinued.

Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. If any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in [Table 14](#) should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require discontinuation of study intervention.

Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in [Table 14](#) should be followed.

Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3.1 and Section 1.3.3 of this appendix). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

$$\text{Corrected calcium} = ([4 - \text{serum albumin in g/dL}] \times 0.8) + \text{serum calcium}$$

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and vitamin D supplementation) until resolution.

Management of Hemorrhage

Instructions in [Table 14](#) should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or Grade 4 fistula.

Management of Osteonecrosis

Perform an oral examination before treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgment of adequate resolution.

ATRA

ATRA dose interruption for participants who experience ATRA-related toxicity will be in accordance with the dose modification guidelines described in Table 3, and in accordance with investigator's assessment of whether ATRA dose interruption is required to manage participant's toxicity. The dose of ATRA in this study is 150 mg/m²/day. Dose may be reduced to 100 mg/m²/day to manage toxicities upon Sponsor consultation and approval (Table 15).

Adverse events will be graded using NCI CTCAE version 5.0. Investigators will decide the probability of the event being related to a single drug or a combination of drugs as to whether dose modification of a single drug or the combination of drugs is required.

Once the ATRA dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Note: If pembrolizumab is permanently discontinued, ATRA must also be discontinued.

Table 15 Dose Modification Guidelines for ATRA-Related Adverse Events

Treatment-Related Toxicity ^{a,b}	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2	Continue treatment	No change
Intolerable Grade 2^c or Grade 3^d		
First occurrence	Interrupt ATRA until resolved to Grade 0-1, or tolerable Grade 2.	Reduce ATRA dose to 50 mg/m ² twice daily (100 mg/m ² daily) x 3 days q3 weeks.
Second occurrence (same toxicity or new toxicity)	Interrupt ATRA.	Further dose reduction should be discussed with Sponsor, otherwise discontinue ATRA ^e .
Grade 4^d: Discontinue Study Intervention^e		

AE=adverse event; ATRA=all-trans retinoic acid; BMI=body mass index; CTCAE=Common Terminology Criteria for Adverse Events; q3w=once every 3 weeks.

Note: For grading see CTCAE version 5.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

- a An interruption of study intervention with ATRA for more than 28 days will require Sponsor approval before study intervention can be resumed.
- b Initiate optimal medical management for headache before any ATRA interruption or dose reduction.
- c Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.
- d For asymptomatic laboratory abnormalities, such as Grade ≥ 3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.
- e If ATRA is discontinued, pembrolizumab may be continued if, in the opinion of the investigator, the toxicity is solely attributable to ATRA.

Toxicity Management of Infusion Reactions Related to MK-7684, MK-1308, or Lenvatinib

MK-7684 (anti-anti-TIGIT)

MK-7684 may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of the infusion. Toxicity management guidelines for infusion reactions should be followed for MK-7684 ([Table 4](#)).

MK-1308

MK-1308 may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of the infusion. Toxicity management guidelines for infusion reactions should be followed for MK-1308 ([Table 4](#)).

Lenvatinib

Not applicable.

ATRA

Not applicable.

10.6.2.15.1.1 Section 6.6.2.1 Other Allowed Dose Interruptions

MK-7684 (anti-TIGIT)

None.

MK-1308

None.

Lenvatinib

If the participant is receiving treatment with lenvatinib and requires surgery during the substudy, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) before surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.

ATRA

None.

10.6.2.15.2 Section 6.6.3 Dose Modification for Overlapping Toxicities

Holding pembrolizumab, MK-7684, or MK-1308 for Arm 1, or pembrolizumab, MK-1308, or lenvatinib for Arm 2 and not the other(s) is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study interventions. For example, if MK-7684 is held due to an AE attributed to that treatment, then pembrolizumab and MK-1308 may continue to be administered. The investigator must appropriately document the attribution of the AE. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, then both study interventions should be held according to recommended dose modifications after consultation with the Sponsor ([Table 3](#)).

For Arm 3, holding ATRA but not pembrolizumab is appropriate, if, in the opinion of the investigator, the toxicity is clearly related to ATRA. However, if pembrolizumab is held,

ATRA must also be held. Furthermore, if a participant discontinues pembrolizumab, they must also discontinue ATRA at that time.

Lenvatinib

Based on the known toxicity profile of lenvatinib, certain treatment-related AEs are uniquely associated with this drug. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab and MK-1308 treatment. However, certain AEs, such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either lenvatinib and/or pembrolizumab and/or MK-1308. Therefore, evaluation of attribution is important for determining the study intervention most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), pembrolizumab is dosed q6w and MK-1308 q6w due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

- If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.
- If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab and MK-1308 should be held.

If the participant recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

If an AE is suspected to be treatment related and is severe/life-threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

3. Participants receiving lenvatinib must discontinue study intervention if any of the following occur:

- ALT or AST $>5 \times$ ULN for more than 2 weeks.
Pembrolizumab will have already been permanently discontinued per [Table 3](#), but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

- ALT or AST $>3 \times$ ULN and (TBL $>2 \times$ ULN or INR >1.5).
Although [Table 3](#) advises pembrolizumab to be withheld (interrupted), and [Table 14](#) advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

10.6.2.16 Section 7.1 Discontinuation of Study Intervention

Interruptions from the protocol-specified treatment ≥ 12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

MK-7684 (anti-TIGIT)

No additional discontinuation criteria are required for MK-7684. Refer to Section 7.1 of this substudy protocol for instructions that apply to discontinuation of study intervention and participant withdrawal.

MK-1308

No additional discontinuation criteria are required for MK-1308. Refer to Section 7.1 of this substudy protocol for instructions that apply to discontinuation of study intervention and participant withdrawal.

Lenvatinib

In the event of nephrotic syndrome, lenvatinib must be discontinued. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

Participants receiving lenvatinib must discontinue study intervention if any of the following occur:

- ALT or AST $>5 \times$ ULN for more than 2 weeks.
Pembrolizumab will have already been permanently discontinued per [Table 3](#), but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
- ALT or AST $>3 \times$ ULN and (TBL $>2 \times$ ULN or INR >1.5).
Although [Table 3](#) advises pembrolizumab to be withheld (interrupted), and [Table 14](#) advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

Refer to Section 7.1 of this substudy protocol for instructions that apply to discontinuation of study intervention and participant withdrawal.

ATRA

No additional discontinuation criteria are required for ATRA. However, it is important to note that if a participant discontinues pembrolizumab, they must also discontinue ATRA at that time. Refer to Section 7.1 of this substudy protocol for instructions that apply to discontinuation of study intervention and participant withdrawal.

10.6.2.17 Section 8.1 Administrative and General Procedures

No additional assessments or procedures are required for MK-7684, MK-1308, or lenvatinib. Refer to the SoA (Section 1.3 of this appendix) and Section 8 of this substudy protocol.

10.6.2.17.1 Section 8.1.8 Study Intervention Administration

10.6.2.17.1.1 Section 8.1.8.1.2 Investigational Agents Administration

MK-7684 (anti-TIGIT)

MK-7684 will be administered on Day 1 of every treatment cycle over a period of approximately 30 minutes for a total of 35 treatment cycles. MK-7684 will be administered approximately 30 minutes after completion of the pembrolizumab infusion.

MK-1308

MK-1308 will be administered on Day 1 of every other treatment cycle (ie, q6w) over a period of approximately 30 minutes for a total of 17 treatment cycles. MK-1308 will be administered approximately 30 minutes after completion of the MK-7684 infusion in Arm 1 and approximately 30 minutes after the completion of the pembrolizumab infusion in Arm 2.

Lenvatinib

Lenvatinib will be administered daily on a 21-day cycle for up to 2 years of treatment. On C1D1, C2D2, C3D1, etc, lenvatinib will be taken 0 to 4 hours after completion of pembrolizumab and MK-1308 administration. Lenvatinib will be taken in the clinic on C1D1, C2D1, C3D1, etc.

Participants may be allowed to continue lenvatinib beyond 2 years, at the investigator's discretion, if there is clinical benefit.

ATRA

ATRA will be administered on 3 days q3w: on Days 1, 2, and 3 of the first cycle and on Days -1, 1, and 2 for all subsequent cycles for up to 2 years of treatment. ATRA should be administered twice daily in the morning and evening. Pembrolizumab is administered on Day 1 of each cycle q6w. On those days where both ATRA and pembrolizumab are administered, pembrolizumab may be infused approximately 30 minutes after the ATRA am dose.

10.6.2.17.2 Section 8.1.8.2 Lenvatinib Compliance

Lenvatinib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

10.6.2.17.3 Section 8.1.8.3 ATRA Compliance

ATRA compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

10.6.2.18 Section 8.2 Efficacy/Immunogenicity Assessments

MK-7684 (anti-TIGIT)

Immunogenicity assessments will not be performed for MK-7684.

MK-1308

Immunogenicity assessments will not be performed for MK-1308.

Lenvatinib

Immunogenicity assessments will not be performed for lenvatinib.

ATRA

Immunogenicity assessments will not be performed for ATRA

10.6.2.19 Section 8.3 Safety Assessments

10.6.2.19.1 Section 8.3.2 Vital Signs

MK-7684 (anti-TIGIT)

No specific vital signs assessments are required for MK-7684. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.2 of this substudy protocol.

MK-1308

No specific vital signs assessments are required for MK-1308. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.2 of this substudy protocol.

Lenvatinib

Vital sign measurements (ie, systolic and diastolic BP [mm Hg], heart rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), weight (kg), and height (cm) will be obtained at the visits designated in the SoA (Section 1.3 and Section 1.3.3 of this appendix) by a validated method.

- BP and heart rate will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.
- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the participant's initial BP is elevated (ie, systolic BP $\geq$ 140 mm Hg or diastolic BP $\geq$ 90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) shows an elevated BP (systolic BP $\geq$ 140 mm Hg or diastolic BP $\geq$ 90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.
- At the C1D8 telephone visit and if required between clinic visits, participants will have BP measured. If the participant does not return to the study site for this BP measurement, BP may be measured, for example, at home or at a local pharmacy, and the results will be reviewed with the investigator or designee. The investigator/site may provide a diary as a tool to aid the participant in collecting BP evaluations between clinic visits. The Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP retest, or other clinically appropriate intervention(s).

ATRA

No specific vital signs assessments are required for ATRA. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.2 of this substudy protocol.

10.6.2.19.2 Section 8.3.3 Electrocardiograms

MK-7684 (anti-TIGIT)

No specific ECG assessments are required for MK-7684. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.3. of this substudy protocol.

MK-1308

No specific ECG assessments are required for MK-1308. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.3. of this substudy protocol.

Lenvatinib

The Fridericia correction method for calculating QTc will be used.

QTc prolongation has been seen in some lenvatinib studies. Monitor electrocardiograms every cycle (as specified in the SoA) in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. These patients are considered high-risk patients. Please refer to the lenvatinib IB.

ATRA

No specific ECG assessments are required for ATRA. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.3. of this substudy protocol.

10.6.2.19.3 Section 8.3.4 Multiple-Gated Acquisition Scan or Echocardiogram

MK-7684 (anti-TIGIT)

No specific MUGA or echocardiogram assessments are required for MK-7684. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.4 of this substudy protocol.

MK-1308

No specific MUGA or echocardiogram assessments are required for MK-1308. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.4 of this substudy protocol.

Lenvatinib

A MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess LVEF as designated in the SoA (Section 1.3 of this appendix). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

ATRA

No specific MUGA or echocardiogram assessments are required for ATRA. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.4 of this substudy protocol.

10.6.2.19.4 Section 8.3.5 Clinical Safety Laboratory Assessments

10.6.2.19.4.1 Section 8.3.5.1 Urine Dipstick

MK-7684 (anti-TIGIT)

No specific urine dipstick assessments are required for MK-7684. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.5.1 of this substudy protocol.

MK-1308

No specific urine dipstick assessments are required for MK-1308. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.5.1 of this substudy protocol.

Lenvatinib

Once participants are randomized/allocated to a lenvatinib-containing investigational treatment arm, urine dipstick testing should be performed at the timepoints specified in Appendix 6, Section 10.6.2.1.3. For participants with proteinuria $\geq 2+$, urine dipstick testing should be performed as clinically indicated until the results are 1+ or negative for 2 consecutive treatment cycles. Urine dipstick testing should be performed locally.

For participants with proteinuria $\geq 2+$, refer to Appendix 6, Section 10.6.2.15.1 for management of proteinuria.

ATRA

No specific urine dipstick assessments are required for ATRA. Refer to the SoA (Section 1.3 of this appendix) and Section 8.3.5.1 of this substudy protocol.

10.6.2.19.5 Section 8.3.6 Pregnancy Testing

MK-7684 (anti-TIGIT)

No specific pregnancy testing assessments are required for MK-7684. Refer to the SoA (Section 10.6.2.1 of this appendix) and Appendix 5 of this substudy protocol.

MK-1308

No specific pregnancy testing assessments are required for MK-1308. Refer to the SoA (Section 10.6.2.1 of this appendix) and Appendix 5 of this substudy protocol.

Lenvatinib

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours of the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation.

ATRA

There is a high risk that a severely deformed infant will result if VESANOID is administered during pregnancy. If it is determined that VESANOID represents the best available treatment for a pregnant woman or a woman of childbearing potential, it must be assured that the participant has received full information and warnings of the risk to the fetus if she were to

be pregnant and of the risk of possible contraception failure and has been instructed in the need to use 2 reliable forms of contraception simultaneously during therapy and for 1 month after discontinuation of therapy, and has acknowledged her understanding of the need for using dual contraception, unless abstinence is the chosen method. Within 24 hours before the institution of VESANOID therapy, the participant should have blood or urine collected for a serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL. When possible, VESANOID therapy should be delayed until a negative result from this test is obtained. When a delay is not possible, the participant should be placed on 2 reliable forms of contraception. Pregnancy testing and contraception counseling should be repeated monthly throughout the period of VESANOID treatment.

10.6.2.20 Section 8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

10.6.2.20.1 Section 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

MK-7684 (anti-TIGIT)

Please follow reporting Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Information described in Section 8.4 of this substudy protocol.

MK-1308

Please follow reporting Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Information described in Section 8.4 of this substudy protocol.

Lenvatinib

Please follow reporting Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Information described in Section 8.4 of this substudy protocol.

ATRA

Please follow reporting Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Information described in Section 8.4 of this substudy protocol.

10.6.2.21 Section 8.5 Treatment of Overdose - Investigational Agents

MK-7684 (anti-TIGIT)

For the purpose of this substudy, an overdose of MK-7684 will be defined as any dose exceeding the prescribed dose by $\geq 20\%$. No specific information is available on the treatment of overdose of MK-7684. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

MK-1308

For the purpose of this substudy, an overdose of MK-1308 will be defined as any dose exceeding the prescribed dose by $\geq 150\%$. No specific information is available on the treatment of overdose of MK-1308. In the event of overdose, MK-1308 should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Lenvatinib

For purposes of this study, an overdose of lenvatinib will be defined as any dose above the protocol-prescribed dose if associated with an AE. There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for differentiated thyroid cancer, RCC, and HCC.

No specific information is available on the treatment of overdose of lenvatinib.

Overdoses associated with lenvatinib should be reported as a nonserious ECI, unless the AE itself meets criteria for an SAE.

All reports of lenvatinib overdose with an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

ATRA

For purposes of this study, an overdose of ATRA will be defined as any dose above the protocol-prescribed dose if associated with an AE. There has been no experience with acute overdosage in humans. The maximal tolerated dose in patients with myelodysplastic syndrome or solid tumors was 195 mg/m²/day. There is no specific treatment in the case of an overdose, however, it is important that the participant be treated in a special hematological unit.

Overdoses associated with ATRA should be reported as a nonserious ECI, unless the AE itself meets criteria for an SAE.

All reports of ATRA overdose with an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

10.6.2.22

CCI

CCI

10.6.2.22.1 Section 8.6.2 Blood Collection for Investigational Agents

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10.7 Appendix 7: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Before RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological progressive disease by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management) (see [Table 6](#) and [Figure 2](#)). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study intervention at site-assessed first radiologic evidence of progressive disease and is not required to have repeat tumor imaging for confirmation of progressive disease by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm progressive disease by iRECIST, per investigator assessment. Images should continue to be sent to the central imaging vendor for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to $\geq 20\%$ and ≥ 5 mm from nadir
Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of nontarget lesion(s) identified at baseline.
- Development of new lesion(s).

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Nontarget.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
 - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared with any prior iUPD time point
 - For nontarget lesions, worsening is any significant growth in lesions overall, compared with a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
 - For new lesions, worsening is any of these:
 - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
 - Visible growth of new nontarget lesions
 - The appearance of additional new lesions
- Any new factor appears that would have triggered progressive disease by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial progressive disease threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is “reset.” This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management After the Confirmatory Imaging

If repeat imaging does not confirm progressive disease per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule. If progressive disease is confirmed, participants will be discontinued from study intervention.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered after consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Appendix 6, Section 10.6.2.1 and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudoproggression Resolves

After resolution of pseudoproggression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
 - Sum of diameters reaches the progressive disease threshold ($\geq 20\%$ and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudoproggression. The nadir is always the smallest sum of diameters seen during the entire substudy, either before or after an instance of pseudoproggression.
- Nontarget lesions
 - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
 - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
 - New lesions appear for the first time
 - Additional new lesions appear
 - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
 - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial progressive disease, with 1 exception: If new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥ 5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

10.9 Appendix 9: AJCC 8th Edition Staging Criteria and Overall Staging Table

The AJCC has designated staging by TNM classification to define melanoma.

Staging tables ([Table 16](#), [Table 17](#), [Table 18](#), and [Table 19](#)) adapted from AJCC 8th edition. Refer to AJCC guidelines for more information [Gershenwald, J. E., et al 2017].

Table 16 Melanoma T Category Definition

T Stage	T Stage Definition (Thickness and Ulceration)
TX	Primary tumor thickness cannot be assessed (ulceration status not applicable)
T0	No evidence of primary tumor (ulceration status not applicable)
Tis	Melanoma in situ (ulceration status not applicable)
T1	≤1.0 mm (ulceration status unknown or unspecified)
T1a	<0.8 mm without ulceration
T1b	<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration
T2	>1.0-2.0 mm (ulceration status unknown or unspecified)
T2a	>1.0-2.0 mm without ulceration
T2b	>1.0-2.0 mm with ulceration
T3	>2.0-4.0 mm (ulceration status unknown or unspecified)
T3a	>2.0-4.0 mm without ulceration
T3b	>2.0-4.0 mm with ulceration
T4	>4.0 mm (ulceration status unknown or unspecified)
T4a	>4.0 mm without ulceration
T4b	>4.0 mm with ulceration

T=primary tumor.

Table 17 Melanoma N Category Definition

N Category	Number of Tumor-involved Regional Lymph Nodes	Presence of In-transit, Satellite, and/or Microsatellite Metastases
NX	Regional Nodes not assessed (exception: pathological N category not required for T1 melanomas, use clinical N information)	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	2 or 3 tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node	
N2a	2 or 3 clinically occult (detected by SLN biopsy)	No
N2b	2 or 3, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	4 or more clinically occult (detected by SLN biopsy)	No
N3b	4 or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	2 or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

N=regional lymph node; SLN=sentinel lymph node.

Table 18 Melanoma M Category Definition

M Category	Anatomic Site	Lactate Dehydrogenase Level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to noncentral nervous system visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

CNS=central nervous system; M=distant metastasis.

Table 19 AJCC Pathological (pTNM) Staging Groups

Staging (AJCC 8th edition)			
0	Tis	N0	M0
IA	T1a	N0	M0
IA	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIA	T3a	N0	M0
IIB	T3b	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIB	T0	N1b, N1c	M0
IIIC	T0	N2b, N2c, N3b, N3c	M0
IIIA	T1a/b-T2a	N1a or N2a	M0
IIIB	T1a/b-T2a	N1b/c or N2b	M0
IIIB	T2b/T3a	N1a-N2b	M0
IIIC	T1a-T3a	N2c or N3a/b/c	M0
IIIC	T3b/T4a	Any N $\geq$ N1	M0
IIIC	T4b	N1a-N2c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

M0=No evidence of distant metastases; N0=No regional metastasis detected including no tumor-involved nodes and no in-transit, satellite, and/or microsatellite metastasis; pTNM=pathological tumor, nodes, and metastasis.

10.10 Appendix 10: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about >50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
ECOG=Eastern Cooperative Oncology Group Source: [Oken, M.M., et al 1982].	

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10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
1L	first-line
ADA	antidrug antibody
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
anti-CTLA-4	anticytotoxic T-lymphocyte-associated protein 4
APaT	all-participants-as-treated
APL	advanced promyelocytic leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATRA	all-trans retinoic acid
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BP	blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B1
C1D1	Cycle 1 Day 1
C/A/P	chest, abdomen, and pelvis
C _{avg}	average concentration over the dosing interval
CD	cluster of differentiation
CD28	cluster of differentiation 28
CHMP	Committee for Medicinal Products for Human Use (CHMP) is the European Medicines Agency committee responsible for human medicines.
CHO	Chinese hamster ovary
CI	confidence interval
CIV	central imaging vendor
C _{max}	maximum drug concentration.
C _{min}	minimum (or trough) drug concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, version 5.0
ctDNA	circulating tumor DNA
CTFG	clinical trial facilitation group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4

Abbreviation	Expanded Term
DC	dendritic cell
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
E-R	exposure-response
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-dimension 5- level
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FSH	follicle stimulating hormone
FT4	free thyroxine
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GITR	glucocorticoid-induced TNFR-related protein
GVHD	graft-versus-host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatic cell carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HUVEC	human umbilical vein endothelial cell
IA	interim analysis

Abbreviation	Expanded Term
IB	Investigator's Brochure
IC ₅₀	mean inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
IDO	indoleamine-(2,3)-dioxygenase
IgG1	immunoglobulin G, subclass 1
IHC	immunohistochemistry
IL-2R	interleukin-2 receptor
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IO	immuno-oncology
iPR	iRECIST partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	iRECIST stable disease
ITT	immunoglobulin tail tyrosine
ITIM	immunoreceptor tyrosine-based inhibitory motif
iUPD	iRECIST unconfirmed progressive disease
IV	intravenous
IVD	in vitro diagnostic
KO	knock-out
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
M&S	modeling and simulation
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
CCI	
MUGA	multiple-gated acquisition

Abbreviation	Expanded Term
NCI	National Cancer Institute
NDA	New Drug Application
NE	not estimable
NK	natural killer (cells)
NK T	natural killer T (cells)
NSCLC	non-small cell lung cancer
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based PK
pCR	pathological complete response
PD-1	programmed cell-death 1
PDGFR	platelet-derived growth factor receptor
PD-L1	programmed cell-death ligand 1
PD-L2	programmed cell-death ligand 2
PET	positron emission tomography
PFS	progression-free survival
Pgp	P-glycoprotein
PK	pharmacokinetic
PO	by mouth (orally)
PP	per protocol
pPR	pathological partial response
PR	partial response
PRES/RPLS	Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome
PRO	patient-reported outcome
pRR	pathological response rate
PT	prothrombin time
PTT	partial thromboplastin time
PVR	poliovirus receptor
PVRL-2	poliovirus receptor-related 2
q2w	every 2 weeks
q3w	every 3 weeks
q6w	every 6 weeks
qd	once daily
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	quality of life
QT	the time between the beginning of the QRS complex and the end of the T-wave
QTc	The QTc interval is the length of time it takes the electrical system in the heart to repolarize, adjusted for heart rate.
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1

Abbreviation	Expanded Term
RFS	recurrence-free survival
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RTKi	receptor tyrosine kinase inhibitor
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SHP-1	src homology 2 domain-containing protein tyrosine phosphatase 1
SHP-2	src homology 2 domain-containing protein tyrosine phosphatase 2
SIM	Site Imaging Manual
SNP	single-nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
T3	triiodothyronine
TCID	tissue culture infectious dose
Teffs	effector T-cells
Tregs	regulatory T-cells
TSH	thyroid-stimulating hormone
TTD	time to true deterioration
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptors
WOCBP	woman/women of childbearing potential

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