Official Protocol Title:	KEYMAKER-U01 Substudy 2: A Phase 2, Umbrella Study with Rolling Arms of Investigational Agents in Combination with Pembrolizumab in Treatment Naïve Patients with PD-L1 Positive Advanced Non-small Cell Lung Cancer (NSCLC)
NCT number:	NCT04165083
Document Date:	04-Oct-2022

Title Page

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Protocol Title: KEYMAKER-U01 Substudy 2: A Phase 2, Umbrella Study with Rolling Arms of Investigational Agents in Combination with Pembrolizumab in Treatment Naïve Patients with PD-L1 Positive Advanced Non-small Cell Lung Cancer (NSCLC)

Protocol Number: 01B-08

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):

IND	CCI [redacted]
EudraCT	2020-001627-14

Approval Date: 04 October 2022

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 08	04-OCT-2022	To update the enrollment status of arms that have finished recruitment. To incorporate amendment changes to align with EU CTR No 536/2014.
Amendment 07	26-MAY-2022	To clarify the myocarditis toxicity description in the Dose Modification and Toxicity Management Guidelines for irAEs per Health Authority request.
Amendment 06	08-FEB-2022	To add a new treatment arm with MK-0482 and to allow flexibility in the number of enrolling participants who have squamous vs. nonsquamous NSCLC.
Amendment 05	28-SEP-2021	To increase the frequency of pregnancy testing per Health Authority request.
Amendment 04	24-MAY-2021	To update the Dose Modification and Toxicity Management Guidelines for irAEs.
Amendment 03	08-FEB-2021	To include KEYMAKER branding, protocol updates, and other minor clarifications.
Amendment 02	22-MAY-2020	To add PK and ADA assessments in response to FDA comments from the initial IND review.
Amendment 01	25-NOV-2019	Changes made in response to FDA comments from the initial IND review.
Original Protocol	13-AUG-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendments:

To update the enrollment status of arms that have finished recruitment.
To incorporate amendment changes to align with EU CTR No 536/2014.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
10.6 Appendix 6: Substudy Combination-specific Requirements	Table 9 Summary of Investigational Agents Available for Randomization,Table 10 Summary of Investigational Agents No Longer Available for Randomization,and Section10.6.1 heading have been updated to clarify that the MK-4830 (ILT4) arm is no longer actively recruiting.	MK-4830 (ILT4) is no longer available for randomization.
1.1 Synopsis, Intervention Groups 4.1.1 Treatment Arms 6.1 Study Intervention(s) Administered 10.6.1.13 Study Intervention(s) Administered 10.6.2.13 Study Intervention(s) Administered	In the study intervention tables, updated the "Use" designations to "Test Product." "AxMP" has been added to the "IMP/NIMP" column header, defined in the abbreviations list, and the footnote regarding IMP and NIMP/AxMP classifications has been updated.	To align with EU CTR No 536/2014.

Section # and Name	Description of Change	Brief Rationale
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 8.4.7 Events of Clinical Interest	Overdose was removed as an ECI.	Overdose is no longer considered an ECI. The Sponsor had considered overdose an ECI for operational reasons. The change is in alignment with EU CTR No 536/2014.
10.3.1 Definitions of Medication Error, Misuse, and Abuse	New section added providing definitions for medication error, misuse, and abuse. Subsequent sections renumbered sequentially.	To align with EU CTR No 536/2014.
10.6.1.1 Section 1.3 Schedule of Activities (MK-4830 [ILT4]) 10.6.2.1 Section 1.3 Schedule of Activities (MK-0482 [ILT3])	In the table row labeled "Tumor Imaging (CT or MRI of chest, abdomen, pelvis)," a cross-reference to Section 8.11.5 has been added to Note "e."	To clarify scheduling of imaging follow-up visits for participants discontinuing from study treatment.
Throughout Document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: KEYMAKER-U01 Substudy 2: A Phase 2, Umbrella Study with Rolling Arms of Investigational Agents in Combination with Pembrolizumab in Treatment Naïve Patients with PD-L1 Positive Advanced Non-small Cell Lung Cancer (NSCLC)

Short Title: Substudy to test investigational agents in combination with pembrolizumab in PD-L1 positive treatment-naïve NSCLC in a rolling arm design

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

Substudy 2 will investigate administration of an investigational agent or combination of investigational agents in combination with pembrolizumab in treatment-naïve participants with PD-L1 TPS ≥1% advanced NSCLC. 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 8.2.1.4 for further details.

Primary Objectives	Primary Endpoints
- To estimate the objective response rate (ORR) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).	- Objective response: complete response (CR) or partial response (PR).
Secondary Objectives	Secondary Endpoints
- To estimate PFS as assessed by the investigator according to RECIST 1.1.	- PFS, defined as the time from date of first dose until either the earliest date of disease progression or death due to any cause, whichever occurs first.
- To evaluate the safety and tolerability of investigational treatment combinations based on proportion of adverse events.	- Adverse events (AEs). - Study intervention discontinuations due to AEs.

Overall Design:

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

Number of Participants:

The study employs a design in which new treatment arms will be open for enrollment on a rolling basis to evaluate new investigational treatment combinations. Therefore, the total number of participants will depend on the number of treatment arms open for enrollment.

CCI [redacted]

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>

<u>Substudy 2</u>

Participant population: Treatment-naïve squamous and nonsquamous NSCLC; biomarker enriched (PD-L1 TPS ≥1%).

Treatment: Pembrolizumab + an investigational agent or combination of investigational agents for a total of 35 cycles.

In this Substudy, a treatment arm refers to a unique investigational agent or a combination of investigational agents added to pembrolizumab. Investigational agents will only be added to this study after an initial evaluation of safety and tolerability when administered alone and in combination with pembrolizumab has been completed and a recommended Phase 2 dose has been identified. There can be 1 or multiple treatment arms open for enrollment at a given time.

<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin</th><th>Treatment Period</th><th>Use</th></tr>
<tr><td rowspan="2">All treatment arms</td><td>Pembrolizumab</td><td>200 mg</td><td>Q3W</td><td>IV Infusion</td><td>35 cycles[a]</td><td>Test Product</td></tr>
<tr><td>Investigational Agent(s)[b]</td><td colspan="3">See Appendix 6</td><td>35 cycles[a]</td><td>Test Product</td></tr>
<tr><td colspan="7">Abbreviations: IV = intravenous(ly); Q3W = every 3 weeks.
a. 35 cycles starting with Cycle 1.
b. Refer to Appendix 6 for specific dosing information on the investigational agent.</td></tr>
</table>

Other current or former name(s) or alias(es) for study intervention(s) are as follows: pembrolizumab (MK-3475 or SCH 900475)

</td></tr>
<tr><td>Total Number</td><td>The total number of treatment arms will depend on the number of investigational agents. Refer to Appendix 6.</td></tr>
<tr><td>Duration of Participation</td><td>

Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact.

After a screening phase of 35 days, each participant will be assigned to receive study intervention in a substudy until disease progression is radiographically documented and, when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years).

After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4.

</td></tr>
</table>

	Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, and confirmed by the site per iRECIST when clinically appropriate, initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

CCI



1.3 Schedule of Activities

Refer to Appendix 6 for the Schedule of Activities (SoA) for each treatment arm.

2 INTRODUCTION

The master protocol (Protocol 3475-U01) is a Phase 2, umbrella study with rolling arms of investigational agents with either pembrolizumab in combination with chemotherapy or with pembrolizumab alone in participants with NSCLC. The master protocol (Protocol 3475-U01) contains a screening component and multiple treatment substudies for participants with treatment-naïve or previously treated squamous and nonsquamous NSCLC. Substudy 2 is specifically designed for treatment-naïve participants with PD-L1 TPS ≥1% squamous and nonsquamous NSCLC.

2.1 Study Rationale

Studies of chemo-immunotherapy combinations for the 1L treatment of patients with advanced stage NSCLC, such as Cohort G of KEYNOTE-021 (KN021), KN189, and KN407, suggest that the combination of chemotherapy and PD-1 receptor therapy provides a clinically meaningful benefit in this patient population compared with chemotherapy alone. Cohort G of KN021 showed that pembrolizumab plus chemotherapy resulted in a significant

increase in ORR, regardless of PD-L1 expression, versus chemotherapy alone (56.7% vs. 30.2%) in patients with nonsquamous NSCLC [Borghaei, H., et al 2018]. KN189 showed a significant and clinically meaningful increase in median PFS (8.8 months vs. 4.9 months) and estimated OS rate at 12 months (69.2% vs. 49.4%) for pembrolizumab plus chemotherapy versus chemotherapy alone in patients with nonsquamous NSCLC. Pembrolizumab plus chemotherapy decreased the risk of death by 51% and reduced the risk of progression or death by 48%. Furthermore, pembrolizumab plus chemotherapy improved the DOR (11.2 months vs. 7.8 months) and confirmed response rate (47.6% vs. 18.9%) compared with chemotherapy alone [Gandhi, L., et al 2018]. Finally, KN407 showed that pembrolizumab plus chemotherapy significantly improved OS (15.9 months vs. 11.3 months), PFS (6.4 months vs. 4.8 months), and ORR (57.9% vs. 38.4%) compared with chemotherapy alone in patients with squamous NSCLC [Paz-Ares, L., et al 2018].

In addition, pembrolizumab monotherapy has shown a clinically meaningful benefit for the 1L treatment of patients with NSCLC who are PD-L1 positive compared with chemotherapy alone. KN024 showed that pembrolizumab monotherapy improved median PFS (10.3 months vs. 6.0 months), estimated rate of OS at 6 months (80.2% vs. 72.4%), ORR (44.8% vs. 27.8%), and the median DOR (not reached vs. 6.3 months) compared with platinum-based chemotherapy in patients with NSCLC with TPS ≥50% [Reck, M., et al 2016]. However, the TPS cutoff has recently been lowered by KN042, which showed that pembrolizumab monotherapy significantly improved OS for participants with NSCLC who have TPS ≥50% (HR 0.69, 95% CI 0.56-0.85), TPS ≥20% (HR 0.77, 95% CI 0.64-0.92), and TPS ≥1% (HR 0.81, 95% CI 0.71-0.93) compared with chemotherapy alone. Additionally, ORR for the entire population (TPS ≥1%) was 27% for pembrolizumab and 27% for chemotherapy [Mok, T. S. K., et al 2019].

Despite these encouraging data, there is still substantial room for improvement. Hence there is a need to improve the treatment options available to these patients. This substudy design provides the framework for testing investigational agents in patients who might benefit from adding these drugs to the backbone of PD-1 receptor blockade. The infrastructure of this study enables the rolling assignment of investigational agents that are entering this Phase 2 study in an efficient and cost-effective fashion to study the impact of each investigational agent in combination with pembrolizumab for these patients in need.

2.1.1 Rationale for Choice of Investigational Agent in Substudy 2

Investigational agents that successfully complete Phase 1 studies with a RP2D, whose mechanisms of action and toxicity profile make them logical candidates for study in Phase 2 in NSCLC (as first-line therapy) will be tested in this Substudy. The candidate investigational agents are currently being evaluated in early phase studies as monotherapy and in combination therapy with pembrolizumab.

See Appendix 6 for the rationale for the investigational agent(s).

2.2 Background

2.2.1 Non-small Cell Lung Cancer (NSCLC)

Refer to the master protocol (Protocol 3475-U01) for background information on NSCLC.

2.2.1.1 Current Treatment Options and Medical Need

Refer to the master protocol (Protocol 3475-U01) for a discussion of the current treatment options and medical need in NSCLC.

2.2.2 Pembrolizumab Pharmaceutical and Therapeutic Background

Refer to the IB/approved labeling for detailed background information on pembrolizumab.

2.2.3 Investigational Agent Pharmaceutical and Therapeutic Background

Refer to Appendix 6 for background information on the investigational agent(s) currently being investigated in this Substudy.

2.3 Benefit/Risk Assessment

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

An advantage of the adaptive design of this Substudy is that it may allow rapid, concurrent evaluation of multiple investigational agents in combination with pembrolizumab in treatment-naïve NSCLC patients. This may identify new combination interventions with improved response rates over those achieved with anti-PD-(L)1 and/or chemotherapy. Therefore, a potential benefit may be faster clinical development of novel interventions that benefit specific patient populations, while reducing exposure of patients to interventions that do not demonstrate improved clinical benefit. The use of a response adaptive design may give participants of this study a better chance to be treated with a more effective investigational agent. Potential risks of these novel combination interventions may be increased toxicity, intolerability, or unanticipated adverse drug reactions.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Substudy 2 will investigate administration of an investigational agent or combination of investigational agents in combination with pembrolizumab in treatment-naïve participants with PD-L1 TPS ≥1% advanced NSCLC. 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 8.2.1.4 for further details.

Objectives	Endpoints
Primary	
• To estimate the objective response rate (ORR) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).	• Objective response: complete response (CR) or partial response (PR).
Secondary	
• To estimate PFS as assessed by the investigator according to RECIST 1.1.	• PFS, defined as the time from date of first dose until either the earliest date of disease progression or death due to any cause, whichever occurs first.
• To evaluate the safety and tolerability of investigational treatment combinations based on proportion of adverse events.	• Adverse events (AEs). • Study intervention discontinuations due to AEs.
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design of Substudy 2

This Substudy is a Phase 2, rolling arm, multicenter, open-label, adaptive design study that will evaluate the efficacy of investigational agents in combination with pembrolizumab for the treatment of advanced NSCLC. Preliminary efficacy will be evaluated using ORR per RECIST 1.1, as confirmed by the investigator.

Eligible participants include those who have not received prior systemic therapy for advanced disease or in whom a regulatory agency-approved targeted therapy is not indicated as 1L therapy based on defined oncogenic mutations (nonsquamous NSCLC only). Substudy 2 requires that participants' tumors express PD-L1 (TPS ≥1%). Participants are stratified by histology (squamous vs. nonsquamous) and will be randomly assigned to 1 of the treatment arm(s) open for enrollment as outlined in Table 1.

In this Substudy, a treatment arm refers to a unique investigational agent or a combination of investigational agents added to pembrolizumab. Investigational agents will only be added to this study 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.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Appendix 6. Details of study procedures are provided in Section 8.

4.1.1 Treatment Arms

This Substudy will have multiple treatment arms added on a rolling basis. Each treatment arm may investigate 1 or more than 1 investigational agent in combination with pembrolizumab. There can be more than 1 treatment arm open for enrollment at any given time. Investigational agents will be added on a rolling basis as described in Section 4.1.4 of the master protocol (Protocol 3475-U01).

Participants who are eligible for more than 1 substudy will be randomized/allocated to a substudy and treatment arm open for enrollment as outlined in Section 6.3.1 of the master protocol (Protocol 3475-U01).

In this Substudy, eligible participants will be assigned to 1 of the treatment arm(s) open for enrollment to receive pembrolizumab 200 mg Q3W plus an investigational agent or a combination of investigational agents for up to 35 cycles as outlined in Table 1.

Table 1 Substudy 2 Treatment Plan

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin	Regimen/ Treatment Period/ Vaccination Regimen	Use
All treatment arms	Pembrolizumab	200 mg	Q3W	IV	35 cycles[a]	Test Product
	Investigational Agent(s)[b]	See Appendix 6			35 cycles	Test Product

Abbreviations: IV = intravenous(ly); Q3W = every 3 weeks.
a. 35 cycles starting with Cycle 1.
b. Refer to Appendix 6 for specific dosing information on the investigational agent(s).

4.1.2 Stratification

Refer to the master protocol (Protocol 3475-U01) for complete details on stratification across substudies.

4.1.3 Randomization

Refer to the master protocol (Protocol 3475-U01) for complete details on randomization to treatment arms across and within substudies.

4.1.4 Criteria for Adding Arms

Refer to the master protocol (Protocol 3475-U01) for complete details on criteria and procedures for adding arms to the Substudy.

New investigational agents will be added to this Substudy through an amendment by adding a new section in Appendix 6, specific for that investigational agent (eg, Appendix 6, Section 10.6). In addition, the Summary of Investigational Agents Available for Randomization (Table 9) will be revised accordingly.

4.1.5 Criteria for Stopping Enrollment Early

Refer to the master protocol (Protocol 3475-U01) for complete details on criteria and procedures for removing arms from the Substudy.

If a treatment arm is either found to be futile or a safety concern is identified, further enrollment to the treatment arm will be closed and the Summary of Investigational Agents Available for Randomization (Table 9) and Summary of Investigational Agents No Longer Available for Randomization (Table 10) will be updated at the next planned protocol amendment.

4.1.6 Efficacy and Safety Evaluations

Refer to the master protocol (Protocol 3475-U01) for a description of efficacy and safety evaluations. Specific procedures to be conducted during the study and the timing of those procedures are outlined in Section 8 and the SoA (Appendix 6), respectively.

Additional details of specific procedures to be performed for each treatment arm (if applicable) are described in Appendix 6.

4.2 Scientific Rationale for Study Design

Refer to the master protocol (Protocol 3475-U01) for the scientific rationale for the study design.

4.2.1 Rationale for Stratification

Refer to the master protocol (Protocol 3475-U01) for a detailed rationale for stratification across each substudy.

4.2.2 Rationale for Randomization

Refer to the master protocol (Protocol 3475-U01) for a detailed rationale for randomization across each substudy. Randomization to treatment arms will occur centrally using an IRT system. More details on randomization are provided in Section 6.3.1 of the master protocol (Protocol 3475-U01).

4.2.3 Rationale for Endpoints

Refer to the master protocol (Protocol 3475-U01) for a detailed rationale for the endpoints of the study.

4.3 Justification for Dose

4.3.1 Rationale for Pembrolizumab Dosing Plan

Refer to the master protocol (Protocol 3475-U01) for the rationale for the pembrolizumab dosing plan.

4.3.2 Rationale for Investigational Agent Dosing Plan

Refer to Appendix 6 for the dosing rationale for each investigational agent.

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 Treatment Arm Termination

1. 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.

2. Plans to modify or discontinue the development of the study intervention.

3. Poor adherence to protocol and regulatory requirements.

4. Quality or quantity of data recording is inaccurate or incomplete.

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 histologically confirmed diagnosis of squamous or nonsquamous NSCLC who have not received prior systemic therapy for their metastatic NSCLC and who are at least 18 years of age on the day of providing documented informed consent will be enrolled in this study.

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

5.1 Inclusion Criteria

Refer to the master protocol (Protocol 3475-U01) for inclusion criteria.

5.2 Exclusion Criteria

Refer to the master protocol (Protocol 3475-U01) for exclusion criteria.

5.3 Lifestyle Considerations

Refer to the master protocol (Protocol 3475-U01) for lifestyle considerations for pembrolizumab. Please refer to Appendix 6 for possible 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, vomiting, or neutropenia.

Please refer to Appendix 6 for possible dietary restrictions for specific investigational agents.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no restrictions. Please refer to Appendix 6 for possible lifestyle considerations for specific investigational agents.

5.3.3 Activity Restrictions

There are no restrictions. Please refer to Appendix 6 for possible lifestyle considerations for specific investigational agents.

5.3.4 Contraception

Refer to the master protocol (Protocol 3475-U01) for a description of contraception requirements. Refer to Appendix 5 for approved methods of contraception.

5.3.5 Pregnancy

Refer to the master protocol (Protocol 3475-U01) for procedures to follow if a participant inadvertently becomes pregnant while on study intervention.

5.3.6 Use in Nursing Women

Refer to the master protocol (Protocol 3475-U01) for instructions on use of study intervention in nursing women.

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

See Appendix 6 for details on contraception requirements and restrictions for the use of investigational agents in pregnant and nursing women.

5.4 Screen Failures

Refer to the master protocol (Protocol 3475-U01) for information on screen failures.

5.5 Participant Replacement Strategy

A participant who discontinues from study treatment or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies (study intervention[s] provided by the Sponsor) will be packaged to support enrollment. 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 study are outlined in Table 2. See also Appendix 6 for specific details on particular investigational agent(s).

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strength	Dosage Levels	Route of Admin.	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
All treatment arms	Experimental	Pembrolizumab (MK-3475)	Biological /Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	35 cycles; Day 1 of each cycle	Test Product	IMP	Central
All treatment arms	Experimental	Investigational Agent(s)	See Appendix 6	See Appendix 6	See Appendix 6	See Appendix 6	See Appendix 6	35 cycles	Test Product	IMP	Central

Abbreviations: EEA = European Economic Area; IMP = Investigational Medicinal Product; IV = intravenous(ly); NIMP/AxMP = Non-Investigational Medicinal Product/Auxiliary Medicinal Product; Q3W = every 3 weeks

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country difference with respect to of the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed. Regimen/Treatment Period of 35 cycles stars with Cycle 1.

Refer to Appendix 6 for specific dosing information on the investigational agent.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 2 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

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 are provided in the Pharmacy Manual.

Details on dose preparation and administration of the investigational agent(s) are described in Appendix 6 and detailed in the Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

Refer to the master protocol (Protocol 3475-U01) for instructions on the handling, storage, and accountability of study intervention.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Refer to the master protocol (Protocol 3475-U01) for a description of study intervention assignment across substudies.

6.3.2 Stratification

CCI [redacted]

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

If there are interruptions in the study intervention schedule or infusion was stopped, the details of and reason for any interruption or infusion cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The

investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy 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.

See Appendix 6 for acceptable and prohibited concomitant medication for the investigational agent(s).

6.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care except for those that are prohibited as described in Section 6.5.2 and Appendix 6, if applicable. All concomitant medication will be recorded on the CRF including all prescription, OTC, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 35 days before the first dose of study intervention and 30 days after the last dose of study intervention should be recorded. Concomitant medications administered after 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.

6.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phases of this study (unless otherwise specified in the protocol):

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy

  Note: Radiotherapy for symptom management is allowed with Sponsor consultation.
- Live vaccines within 30 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, 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.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids except when used for the following purposes:
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - For the prevention of emesis
    - To premedicate for IV contrast allergies
    - To treat COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
    - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease

If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator is to discuss prohibited medication/vaccination with the Sponsor's Clinical Director. 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.

6.5.3 Rescue Medications and Supportive Care for the Management of AEs With Potential Immunologic Etiology

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 are outlined along with the dose modification guidelines in Section 6.6.1, Table 3. 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 study intervention.

Note: If after the evaluation of the event, it is determined not to be related to study intervention, the investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

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

6.5.4 Rescue Medications and Supportive Care for Investigational Agent

See Appendix 6 for details on specific investigational interventions.

6.6 Dose Modification (Escalation/Titration/Other)

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

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination 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 monotherapy, coformulation, or IO combination 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 monotherapy, coformulation, or IO combination 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.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, coformulations, or IO combinations, pembrolizumab monotherapy, coformulations, or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

In these cases where the toxicity is attributed to pembrolizumab coformulations or IO combinations, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, coformulations, or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, coformulations, or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, pembrolizumab monotherapy, coformulations, or IO combinations may be restarted at the discretion of the investigator.

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

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 ≤ 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 ≤ 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 ≥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]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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]		
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	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		
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 to5.0 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).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations or IO Combinations

Pembrolizumab monotherapy, coformulations or IO combinations 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 monotherapy, coformulations or IO combinations associated infusion reactions are provided in Table 4.

Table 4 Pembrolizumab Monotherapy, Coformulations or IO Combinations 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/hr to 50 mL/hr). 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 drug intervention.
		Participant may be premedicated 1.5 h (±30 minutes) before infusion of study intervention with:
		Diphenhydramine 50 mg po (or equivalent dose of antihistamine).
		Acetaminophen 500-1000 mg po (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: o Epinephrine** o IV fluids o Antihistamines o NSAIDs o Acetaminophen o Narcotics o Oxygen o Pressors o 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 drug intervention.	No subsequent dosing
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 Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Dose Modification for Investigational Agent Intervention

See Appendix 6 for details on dose modification for specific investigational agents. If treatment with the investigational agent and pembrolizumab is interrupted or discontinued, treatment with pembrolizumab may continue.

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 drugs, and initiate management as

outlined in Section 6.6.1, Section 6.6.2, and Appendix 6 (for the investigational agent). If toxicity does not improve, the investigator should consider discontinuing the participant.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

Refer to the master protocol (Protocol 3475-U01) for information on clinical supplies disclosure.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, 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 still continue to participate in the study as specified in the SoA (Appendix 6) and Section 8.11.3.

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 study 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 study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.

  Note: refer to Appendix 6 for specific investigational agent criteria.

- 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.

- Confirmed radiographic disease progression outlined in Section 8.2 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

- Completion of 35 treatments of protocol-defined pembrolizumab + investigational agent.

  Note: The number of treatments is calculated starting with the first dose.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, 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 study 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.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study 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 study 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 study-related medical decisions must be made by an investigator who is a qualified physician.
- 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 informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

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 study.

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

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

At the time of Screening study participants will be required to sign the main study consent, which describes the general aspects of the study including the possible substudies the participant could be randomly assigned to and the risk language for pembrolizumab.

Informed Consent Addendum

Once the participant is randomly assigned to a treatment arm within this Substudy, but before dosing, the participant will be required to sign an additional consent. This second consent will be an addendum to the main study consent and will describe the risk language for the specific investigational agent the participant will receive.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

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 the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study 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 allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

8.1.4.1 General Medical History

Refer to the master protocol (Protocol 3475-U01) for a description of the information collected as medical history. Medical history will be captured at the time point specified in the SoA (Appendix 6).

8.1.4.2 Lung Cancer History

Refer to the master protocol (Protocol 3475-U01) for a description of the information collected as lung cancer history. Lung cancer history will be captured as the time point specific in the SoA (Appendix 6).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

Refer to the master protocol (Protocol 3475-U01) for a description of the information collected on prior medications. Prior medications will be captured at the time points specified in the SoA (Appendix 6).

8.1.5.2 Concomitant Medications

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

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

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study treatment(s), the study treatment(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 the study treatment, the 30-day Safety Follow-up Visit should occur before the first dose of the new therapy.

8.1.6 Assignment of Screening Number

Refer to the master protocol (Protocol 3475-U01) for information on assignment of the screening number.

8.1.7 Assignment of Treatment/Randomization Number

Refer to the master protocol (Protocol 3475-U01) for information on assignment of the treatment/randomization number.

8.1.8 Study Intervention Administration

Administration of study intervention will be monitored by the investigator and/or study 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 3 days of allocation/randomization.

8.1.8.1.1 Pembrolizumab Administration

Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each treatment cycle. 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 Agent Administration

See Appendix 6 and 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 study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study 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.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the study. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

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

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

Refer to Appendix 6 for required immunogenicity assessments for pembrolizumab and specific investigational agents.

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

Scans may be collected for possible future analysis by BICR.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for scan collection and storage for possible future transmission to the central imaging vendor can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

Note: For the purposes of assessing tumor scans, 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 scans are required for all participants at Screening. MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Deidentified copies of all scans for all study participants that might be required for later independent review will be held at the sites. Sites may be instructed to submit scans to a central imaging vendor once a treatment combination has met the criteria for superiority. Scans that might be required include all scheduled scans, unscheduled scans (obtained for any reason) that indicate disease progression (in the judgment of the investigator), and any unscheduled scans used to support initial determination or subsequent confirmation of objective response.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 35 days before the date of the first dose of treatment.

Tumor scans performed as part of routine clinical management are acceptable for use as screening tumor scans if it is of diagnostic quality and performed within 35 days before first treatment dose.

Brain Scans

Brain scans are performed to document the stability of existing metastases. MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

Participants 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) for at least 2 weeks before the first dose of study treatment. 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 study initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability. For participants with stable brain metastases enrolled in the study, the baseline brain image must be held at the site for possible future analysis.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 6 weeks (42 days ±7 days) from the date of first dose. The second on-study scan should be performed at 12 weeks (84 days ±7 days) from the date of first dose. Subsequent scans should be performed every 9 weeks (63 days ±7 days) for the first year (until Week 48), after which the scan interval increases to every 12 weeks (84 days ±7 days) or more frequently if clinically indicated. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Scans are to be performed until disease progression is identified by the investigator (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 held at the sites.

Objective response should be confirmed by a repeat scan at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

On-study brain scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain lesions existed at baseline).

When radiological disease progression is identified by the investigator in clinically stable participants, disease progression is to be confirmed by another set of scans performed 4 to 8 weeks later, per iRECIST guidelines (Section 8.2.1.5).

If disease progression is not confirmed, clinically stable participants are to continue study intervention until progression is confirmed. Participants are to return to their regular scan schedule. If the next scheduled scan will occur in less than 4 weeks, this scheduled scan may be skipped.

If disease progression is confirmed, study intervention will be discontinued. Exceptions are detailed in Section 8.2.1.5.

8.2.1.3 End-of-Treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of treatment discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of first dose, refer to Section 8.2.1.2.

Scans are to be continued until one of the following conditions are met: start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, 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.

If disease progression is established by the investigator, the process continues as follows:

- Investigator judgment will determine action
- If the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed. In addition, the following is to occur:
    - Continue scans per protocol schedule (the next scheduled scan should be ≥4 weeks from most recent scan acquired)

For the purpose of this decision process, lack of clinical stability is defined as:

- Unacceptable toxicity
- Clinical signs or symptoms indicating clinically significant disease progression
- Decline in performance status
- Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

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 [Seymour, L., et al 2017]. When clinically stable, participants may continue study intervention beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in Appendix 9. iRECIST reflects that some participants can have a transient tumor flare after the start of immunotherapy then experience subsequent disease response. This data will be captured in the clinical database.

- If participant is clinically stable (refer to Section 8.2.1.4), continue study intervention per protocol
    - Perform scans 4 to 8 weeks after RECIST 1.1 progression
    - Continue investigator assessment per iRECIST
- If the participant is not clinically stable, best medical practice is to be applied

8.2.2 Quality-of-Life Assessments

Not applicable for this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (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.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening Period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in the SoA (Appendix 6). After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in the SoA (Appendix 6), the investigator or qualified designee will perform a directed physical examination as

clinically indicated before the administration of the study intervention. New clinically significant abnormal findings should be recorded as AEs.

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at Screening, before the administration of each dose of study treatment and during the follow-up period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight will be monitored as per vital signs. Height will be measured at Visit 1 only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECG is specified in the SoA (Appendix 6). Clinically significant abnormal findings at baseline should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

8.3.4 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 study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All 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 study 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.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (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 Study Laboratory Manual. Refer to the SoA (Appendix 6) for the timing of laboratory assessments.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy at Screening, within 72 hours of the first dose of study intervention, and every other cycle thereafter, as specified in the SoA (Appendix 6). Additional urine/serum pregnancy tests may be performed if clinically warranted, or as defined by local regulations. Following cessation of treatment, monthly pregnancy testing should be conducted as per local guidelines for up to 120 days after the last dose of pembrolizumab and investigational agent.

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.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at Screening, before the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Appendix 6).

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.

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 allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause 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 treatment allocation/randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization 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, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days after 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 drug related.

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

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 5.

Table 5 Reporting Time Periods for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation Through Protocol-Specified Follow-up Period**	**Reporting Time Period: After the Protocol-Specified Follow-up Period**	**Timeframe to Report Event and Follow-up Information to SPONSOR:**
Nonserious Adverse Event (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
Serious Adverse Event (SAE) including Cancer 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
Event of Clinical Interest (ECI) (requires regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (does 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

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 allocated/randomized 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) 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 the study. Any suspected endpoint which on 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 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

An elevated AST or ALT laboratory value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin laboratory value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Refer to Appendix 6 for the definition and treatment of an overdose associated with investigational agents.

8.6 Pharmacokinetics

Refer to Appendix 6 for PK collection in each treatment arm, if applicable.

8.7 Pharmacodynamics

Refer to Appendix 6 for pharmacodynamic sample collection in each treatment arm, if applicable.

8.8 Biomarkers

Refer to the master protocol (Protocol 3475-U01) for a description of the samples collected for biomarker analyses. Samples will be collected at the time points outlined in the SoA (Appendix 6).

Sample collection, storage and shipment instructions for these specimens will be provided in the Operations/Laboratory Manual.

8.8.1 Planned Genetic Analysis Sample Collection

Refer to the master protocol (Protocol 3475-U01) for a description of the samples collected for planned genetic analyses. Samples will be collected at the time points outlined in the SoA (Appendix 6).

Sample collection, storage, and shipment instruction for these specimens will be provided in the Operations/Laboratory Manual.

8.8.2 Tumor Tissue Collection

An archival tumor tissue sample or a newly obtained core or excisional biopsy of a tumor lesion not previously irradiated must be provided as outlined in the master protocol (Protocol 3475-U01).

Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

Refer to the master protocol (Protocol 3475-U01) for a description of the samples that may be retained for future biomedical research.

Refer to Appendix 7 for information regarding the collection and management of specimens for future biomedical research.

8.10 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 study site personnel for all participants throughout the study. 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 allocation through 90 days after cessation of study treatment, or 30 days after cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier.

8.11 Visit Requirements

Visit requirements are outlined in the SoA (Appendix 6). Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing 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 35 days before the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 10 days before the first dose of study intervention. An exception is hepatitis and HIV testing which may be performed up to 35 days before the first dose of study intervention if mandated by local health authorities (see Table 7 in Appendix 2).

- Evaluation of ECOG is to be performed within 7 days before the first dose of study intervention.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 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 study site laboratory).

- An archival tumor sample either should have been collected within 5 years or within the interval from completion of last treatment but before entering the screening period. Newly obtained core or excisional biopsy of a tumor lesion not previously irradiated may be obtained within 90 days of treatment initiation. Biopsies obtained before receipt of adjuvant/neoadjuvant chemotherapy will be permitted if recent biopsy is not feasible.

Screening procedures may be repeated after consultation with the Sponsor.

8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Appendix 6). Specific procedure-related details are provided in Section 8.

8.11.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in the SoA (Appendix 6). Additional details regarding participant withdrawal and discontinuation are presented in Section 8.1.9.

8.11.4 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 initiation of a new anticancer treatment, whichever comes first.

8.11.5 Imaging Follow-up Visit(s)

Participants who discontinue treatment for reasons other than verified PD should continue with imaging assessments per the protocol-defined schedule until: (1) PD is verified or further confirmed by the investigator, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, or (5) study conclusion or early termination, whichever occurs first.

8.11.5.1 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 at 6 weeks (42 ±7 days), at 12 weeks (84 ±7 days), and then every 9 weeks (63 days ±7 days) for ~1 year (until Week 48), and then every 12 weeks (84 days ±7 days) after Year 1 using the same imaging method used during treatment to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

8.11.5.2 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 approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

1. For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).

2. For participants who perform assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment Follow-up Visit has been performed.

8.11.6 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested before but not limited to an eDMC

review, interim and/or final analysis. On Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section outlines the statistical analysis strategies and procedures for the primary and secondary objectives of Substudy 2, also summarized in the master protocol of the umbrella study (Protocol 3475-U01). Exploratory and other nonconfirmatory analyses for this Substudy will be outlined in a separate supplemental sSAP for this protocol.

If, after the umbrella study has begun, changes are made to the primary or secondary objectives of this Substudy, or the statistical methods related to those objectives, the master protocol and this protocol will be amended (consistent with ICH Guideline E9). Changes to the exploratory or other nonconfirmatory analyses of this Substudy, made after this protocol has been finalized, but before the conduct of any analyses, will be documented in the sSAP as needed and referenced in the CSR for each treatment arm in this Substudy. Post hoc exploratory analyses will be clearly identified in the CSR of each treatment arm.

Full details are in the SAP, Section 9.6.

Study Design Overview	This is an open-label, Phase 2 study in treatment-naïve participants with PD-L1 TPS ≥1% advanced or metastatic (squamous or nonsquamous) NSCLC. All treatment arms in this Substudy receive 35 cycles of pembrolizumab + an investigational agent or combination of investigational agents. Investigational agents will be added to and removed from the Substudy on a rolling basis.
Treatment Assignment	This is an open-label study and randomization will occur at the overall umbrella study level as described in the master protocol (Protocol 3475-U01). This Substudy will include only PD-L1 TPS ≥1% participants CCI [redacted]. Randomization will be conducted to all treatment arms open for enrollment within each appropriate biomarker and histologic type combination as outlined in the master protocol (Protocol 3475-U01). Although initially equal randomization will be used, the randomization ratio may be changed before or after the interim analysis to allocate more participants to the arm(s) with compelling efficacy observed from medical monitoring of study. Details on the response adaptive randomization will be described in the sSAP.
Analysis Populations	Efficacy (Primary): FAS Efficacy (Secondary): APaT Safety (Secondary): APaT
Primary Endpoints	1. Objective response per RECIST 1.1

Secondary Endpoint(s)	1. PFS 2. AE 3. Study intervention discontinuations due to AEs
Statistical Methods for Efficacy Analyses	For this Substudy, the posterior probability that the true ORR is greater than 30% in each treatment arm will be provided separately, along with the point estimate and the 90% CI for the ORR. The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment arm, separate or pooling both histologic types. The corresponding 90% CI using the Greenwood's formula will also be provided.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate.
Interim Analyses	CCI [redacted]
Multiplicity	
Sample Size and Power	

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics Department of the Sponsor.

The study is open-label, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned.

9.3 Hypotheses/Estimation

The objectives and the hypotheses of the study are outlined in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Objective response per RECIST 1.1 evaluated by the investigator is the primary efficacy endpoint. An objective response is a CR or PR with confirmation.

The secondary efficacy endpoint is PFS per RECIST 1.1 evaluated by the investigator.

PFS per RECIST 1.1 is defined as the time from first dose to the first documented disease progression according to RECIST 1.1, as assessed by the investigator, or death due to any cause, whichever occurs first. CCI [redacted]

Upon initial disease progression, participants will continue study intervention until a confirmed progression according to iRECIST is made.

CCI [redacted]

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.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

CCI [redacted]

9.5.2 Safety Analysis Population

CCI [redacted]

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the exploratory endpoints will be described in the sSAP.

9.6.1 Statistical Methods for Efficacy Analysis

In this Substudy, the ORR estimates and associated exact 90% CI will be reported in each treatment arm, pooling both histologic types.

The posterior probability that the true ORR is greater than 30% will be evaluated in each treatment arm.

The posterior probability of ORR will be obtained from its posterior distribution, which is inferred from the observed response rates assuming a prior distribution for the ORR. A noninformative Beta (1, 1) prior distribution for the ORR will be used, which gives no particular preference to any ORR values.

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group, separate or pooling both histologic types. The corresponding 90% confidence interval using the Greenwood's formula will also be provided.

Analysis results may be reported for one or multiple treatment arms at a time.

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, ECG measurements, and physical examinations. Safety will be evaluated by treatment arm.

9.6.3 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

CCI

[redacted]

CCI

[redacted]

9.8 Multiplicity

CCI

[redacted]

9.9 Sample Size and Power Calculations

CCI

[redacted]

CCI



9.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the trial. Any deviation from protocol-directed administration will be reported.

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 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. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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.

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 fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees 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. 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

Not applicable for this study.

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 particular 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 7 will be performed by the local laboratory.
- After Day 1 of Cycle 1, collection of samples for predose laboratory assessments may be performed up to 3 days (72 hours) before dosing in subsequent cycles.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the master protocol (Protocol 3475-U01).
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes[a]	WBC[a] count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)[b]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Carbon dioxide (CO_2 or bicarbonate)[c]	Chloride	Phosphorous
	Creatinine or creatinine clearance[d]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	Thyroid-stimulating hormone (TSH)
	Triiodothyronine (T3)[e]	Free thyroxine (FT4)		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone (FSH) and estradiol (as needed in women of nonchildbearing potential only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP) • Serology (HIV antibody, hepatitis B surface antigen [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. • Coagulation factors (PT or INR and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.
Abbreviations: aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; T3 = triiodothyronine; US = United States; WBC = white blood cell; WOCBP = women of childbearing potential. 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 the local standard of care. d. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine. e. T3 is preferred, if not available, Free T3 may be tested.	

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 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 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.

  Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE.

- 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.

10.3.3 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.

10.3.4 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 timeframe 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

10.3.5 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

- 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.

10.3.6 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 for this study.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

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

10.5.2 Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol-defined time frame in Section 5.1 of the master protocol (Protocol 3475-U01):

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a woman of childbearing potential 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 penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8 during the protocol-defined time frame in Section 5.1 of the master protocol (Protocol 3475-U01).

Table 8 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen- containing) hormonal contraception [b, c]
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
  ○ Injectable

• Progestogen-only hormonal contraception [b, c]
  ○ Oral
  ○ Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
Vasectomized partner • A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [a] Typical use failure rates are lower than perfect-use failure rates (ie, when used consistently and correctly). [b] If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of study treatment. [c] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

After initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the SoA, and as required locally.

10.6 Appendix 6: Substudy Combination-specific Requirements

CCI

[redacted]

10.6.1 MK-4830 (ILT4) Investigational Agent Information Summary - ARM NO LONGER ACTIVELY ENROLLING

Procedures and assessments specific for MK-4830 (ILT4) are detailed in the following sections. Refer to the main body of the protocol for general aspects that govern the overall conduct of the study.

10.6.1.1 Section 1.3 Schedule of Activities (MK-4830 [ILT4])

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

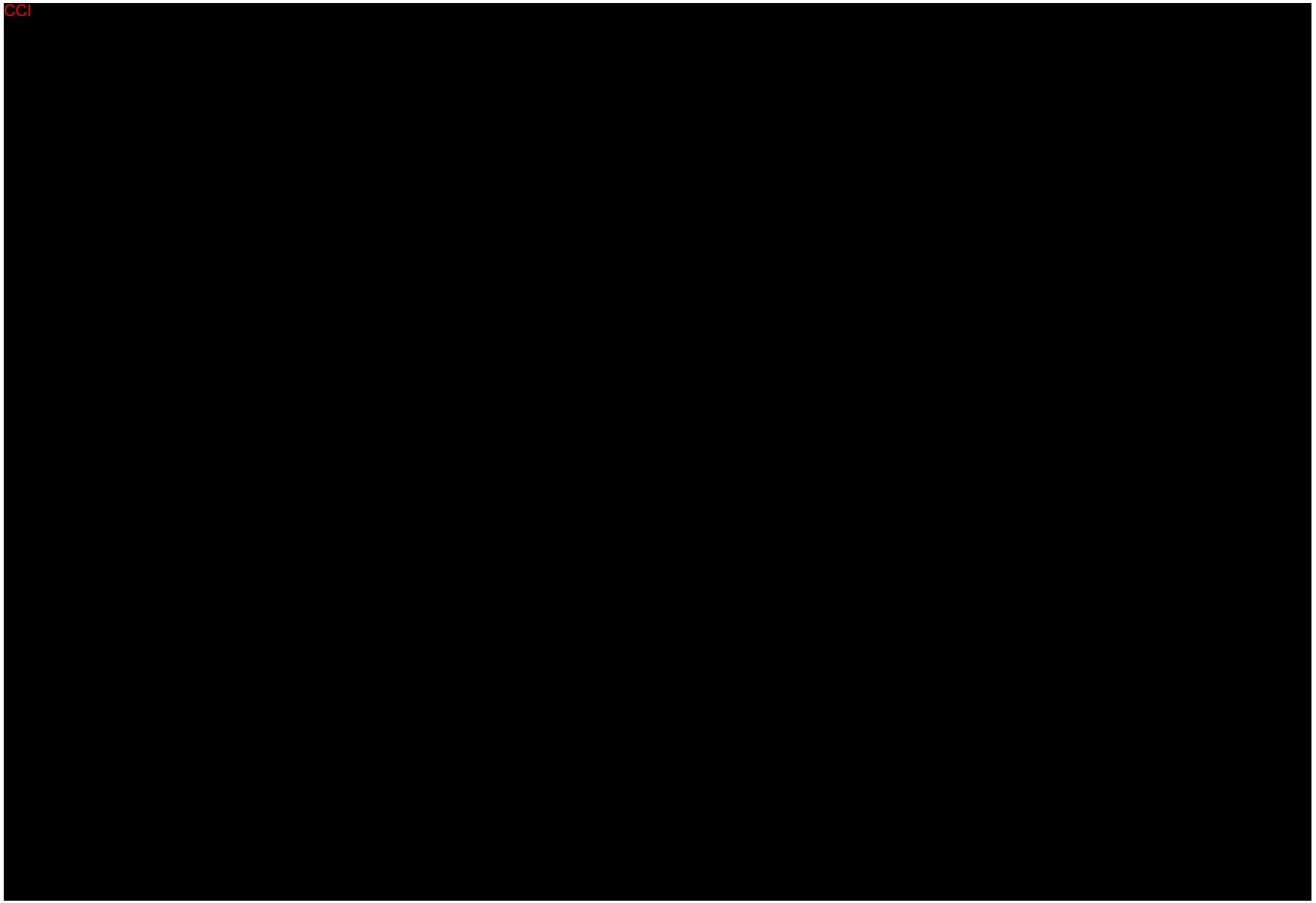
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10.6.1.2 Section 2.2.3 MK-4830 Pharmaceutical and Therapeutic Background

CCI

[redacted]

ILT4 is an inhibitory member of the LILR family that is expressed on myeloid and dendritic cells [Colonna, M., et al 1997] [Colonna, M., et al 1998] [Fanger, N.A., et al 1998]. ILT4 binds MHC class I molecules including HLA-G [Allan, D.S., et al 1999] [Shiroishi, M., et al 2003] [Shiroishi, M., et al 2006]. HLA-G can directly inhibit immune cell function including cytolysis, proliferation, maturation, and chemotaxis [Lin, A. 2015] [Morandi, F., et al 2014]. ILT4 and HLA-G are reported to have high expression in multiple tumor types [Lui, J., et al 2014] [Loumagne, L., et al 2014]. The interaction of ILT4 with HLA-G promotes signaling through immunoreceptor tyrosine-based inhibitory motifs via activation of Src-homology 2 domain-containing phosphatase-1 (SHP-1). This signaling can antagonize immunoreceptor tyrosine-based activation motif receptor-mediated activations of myeloid cells [Colonna, M., et al 1998]. ILT4 signaling is also associated with induction of tolerogenic phenotypes in antigen presenting cells and was shown to promote HLA-G-dependent Type 1 regulatory T-cell development [Gregori, S., et al 2010]. ILT4 signaling may directly inhibit the function of monocytes, dendritic cell and neutrophils, thus impairing the innate immune antitumor response.

CCI

[redacted]

10.6.1.3 Section 2.2.3.1 Preclinical Studies With MK-4830

CCI

[redacted]

CCI

[redacted]

10.6.1.4 Section 2.2.3.2 Ongoing Clinical Studies With MK-4830

CCI

[redacted]

CCI

[redacted]

Clinical PK/Pharmacodynamic Results

CCI

[redacted]

Clinical Safety Results

CCI

[redacted]

Clinical Efficacy Results

CCI

[redacted]

CCI

[redacted]

10.6.1.5 Section 2.2.3.3 Scientific Rationale for the Combination of MK-4830 and Pembrolizumab

Immunotherapy has drastically improved treatment rates of some cancers. However, tumors have several mechanisms to limit an immune response and escape immunosurveillance. MDSC in the tumor microenvironment contribute greatly to tumor immune evasion through multiple mechanisms including suppression of local T-cell activation and proliferation [Adah, D., et al 2016]. CCI

[redacted]

CCI

[redacted]

10.6.1.6 Section 4.1.1 Treatment Arms

Arm 1

CCI [redacted]

10.6.1.7 Section 4.3.3 Rationale for MK-4830 Dosing Plan

The dose escalation and confirmation for MK-4830 dosing, using the ATD and mTPI design in Study MK-4830-001, is complete and no DLTs were observed. Based on the safety and PK data from Study MK-4830-001, the RP2D of MK-4830 to be used as both monotherapy and in combination with pembrolizumab is 800 mg administered Q3W.

Refer to Sections 5 and 6 of the MK-4830 IB for a detailed description of the Effects in Humans and Guidance for the Investigator, respectively.

10.6.1.8 Section 5.3 MK-4830 Lifestyle Considerations

CCI [redacted]

10.6.1.9 Section 5.3.1 Meals and Dietary Restrictions

CCI [redacted]

10.6.1.10 Section 5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

CCI [redacted]

10.6.1.11 Section 5.3.3 Activity Restrictions

CCI [redacted]

10.6.1.12 Section 5.3.7 Investigational Agent Contraception, Pregnancy, and Use in Nursing Women

CCI [redacted]

10.6.1.13 Section 6.1 Study Intervention(s) Administered

CCI

[redacted]

10.6.1.14 Section 6.2.1 MK-4830 Dose Preparation

CCI [redacted]

10.6.1.15 Section 6.2.2 MK-4830 Handling, Storage, and Accountability

Refer to Section 6.2.2 of the master protocol (Protocol 3475-U01) for accountability instructions.

CCI [redacted]

10.6.1.16 Section 6.3.1 Intervention Assignment

Participants eligible for Substudy 2 will be randomly assigned to Treatment Arm 1 centrally using an IRT system.

10.6.1.17 Section 6.5.2 Prohibited Concomitant Therapy

CCI [redacted]

10.6.1.18 Section 6.5.4 Rescue Medications and Supportive Care for MK-4830

CCI [redacted]

10.6.1.19 Section 6.6.2 Dose Modifications for MK-4830

CCI [redacted]

10.6.1.20 Section 6.6.3 Dose Modification for Overlapping Toxicities

There are no additional dose modification instructions for overlapping toxicities. Refer to Section 6.6.3 of the protocol.

10.6.1.21 Section 7.1 Discontinuation of Study Intervention

CCI [redacted]

10.6.1.22 Section 8 Study Assessment and Procedures

CCI [redacted]

10.6.1.23 Section 8.1.8.1.2 MK-4830 Administration

CCI [redacted]

10.6.1.24 Section 8.5 Treatment of Overdose

CCI [redacted]

10.6.1.25 Section 8.6 Pharmacokinetics

Refer to the SoA for PK collection timepoints.

10.6.1.26 Section 8.7 Pharmacodynamics

Not applicable for this study.

10.6.1.27 References

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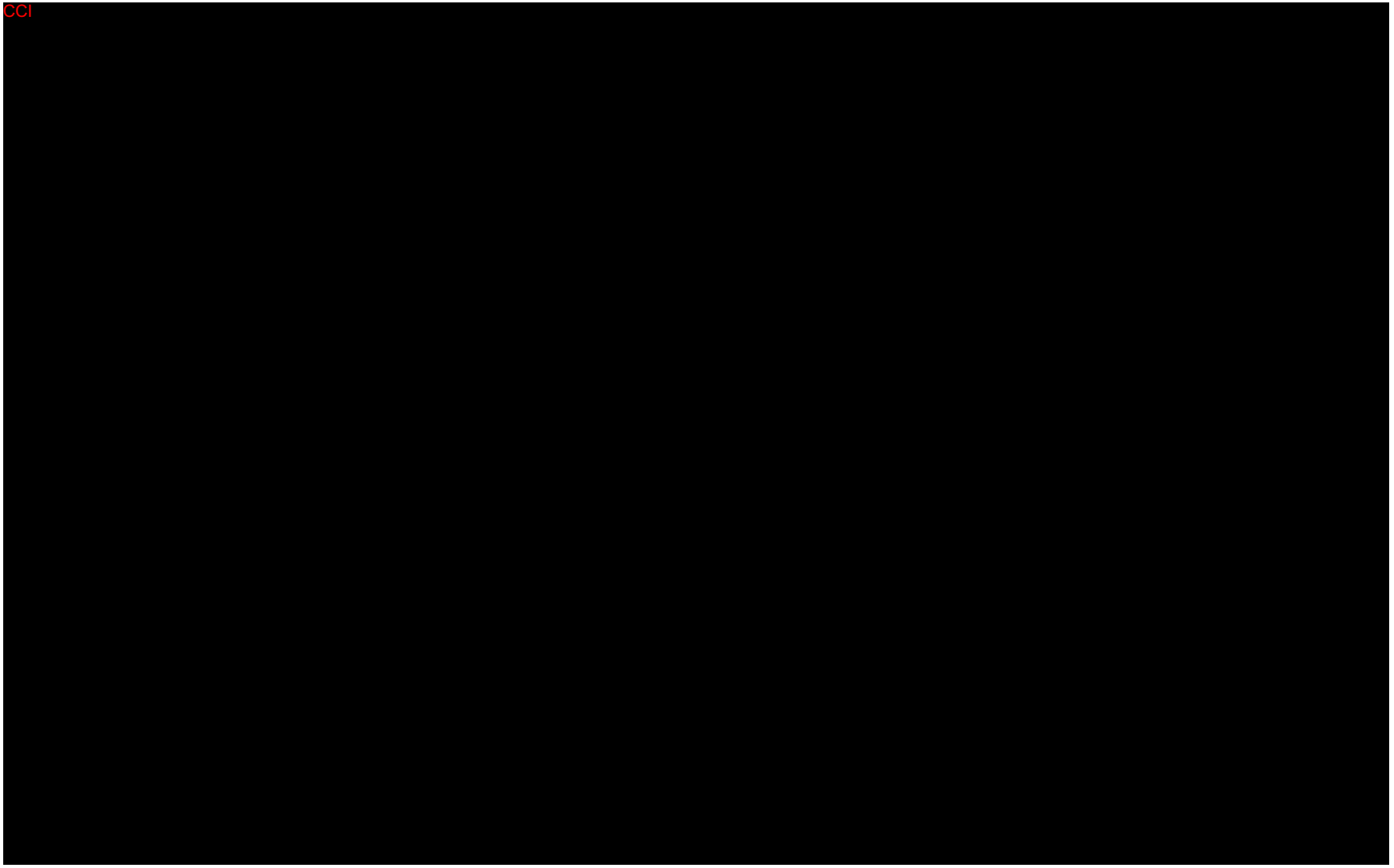
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10.6.2 MK-0482 (ILT3) Investigational Agent Information Summary

Procedures and assessments specific for MK-0482 (ILT3) are detailed in the following sections. Refer to the main body of the protocol for general aspects that govern the overall conduct of the study.

10.6.2.1 Section 1.3 Schedule of Activities (MK-0482 [ILT3])

CCI



CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

10.6.2.2 Section 2.2.3 MK-0482 Pharmaceutical and Therapeutic Background

CCI

[redacted]

10.6.2.3 Section 2.2.3.1 Preclinical Studies With MK-0482

CCI

[redacted]

10.6.2.4 Section 2.2.3.2 Ongoing Clinical Studies With MK-0482

CCI

[redacted]

CCI

[redacted]

Clinical PK and Pharmacodynamic Results

CCI

[redacted]

Clinical Safety and Efficacy Results

CCI

[redacted]

Additional Ongoing Clinical Studies

CCI [redacted]

10.6.2.5 Section 2.2.3.3 Scientific Rationale for the Combination of MK-0482 and Pembrolizumab

Given the evidence demonstrating that the ILT3 pathway may be a key regulatory element responsible for the induction and maintenance of tumor immune tolerance, inhibitors of ILT3 may provide an innovative and tractable method to treat malignancies in combination with other immunotherapy-based strategies such as inhibitors of the PD-1/PD-L1 axis. CCI [redacted]

CCI [redacted]

10.6.2.6 Section 4.1.1 Treatment Arms

Arm 2

CCI [redacted]

CCI

[redacted]

10.6.2.7 Section 4.3.3 Rationale for MK-0482 Dosing Plan

CCI

[redacted]

10.6.2.8 Section 5.3 MK-0482 Lifestyle Considerations

CCI

[redacted]

10.6.2.9 Section 5.3.1 Meals and Dietary Restrictions

CCI

[redacted]

10.6.2.10 Section 5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

CCI

[redacted]

10.6.2.11 Section 5.3.3 Activity Restrictions

CCI

[redacted]

10.6.2.12 Section 5.3.7 Investigational Agent Contraception, Pregnancy, and Use in Nursing Women

CCI

[redacted]

10.6.2.13 Section 6.1 Study Intervention(s) Administered

Table 2 Study Intervention

CCI

10.6.2.14 Section 6.2.1 MK-0482 Dose Preparation

CCI [redacted]

10.6.2.15 Section 6.2.2 MK-0482 Handling, Storage, and Accountability

CCI [redacted]

10.6.2.16 Section 6.3.1 Intervention Assignment

CCI [redacted]

10.6.2.17 Section 6.5.2 Prohibited Concomitant Therapy

CCI [redacted]

10.6.2.18 Section 6.5.4 Rescue Medications and Supportive Care for MK-0482

CCI [redacted]

10.6.2.19 Section 6.6.2 Dose Modifications for MK-0482

CCI [redacted]

10.6.2.20 Section 6.6.3 Dose Modification for Overlapping Toxicities

CCI [redacted]

10.6.2.21 Section 7.1 Discontinuation of Study Intervention

CCI [redacted]

10.6.2.22 Section 8 Study Assessment and Procedures

CCI [redacted]

10.6.2.23 Section 8.1.8.1.2 MK-0482 Administration

CCI [redacted]

10.6.2.24 Section 8.5 Treatment of Overdose

CCI [redacted]

10.6.2.25 Section 8.6 Pharmacokinetics

Refer to the SoA for PK collection timepoints.

10.6.2.26 Section 8.7 Pharmacodynamics

Not applicable for this study.

10.6.2.27 References

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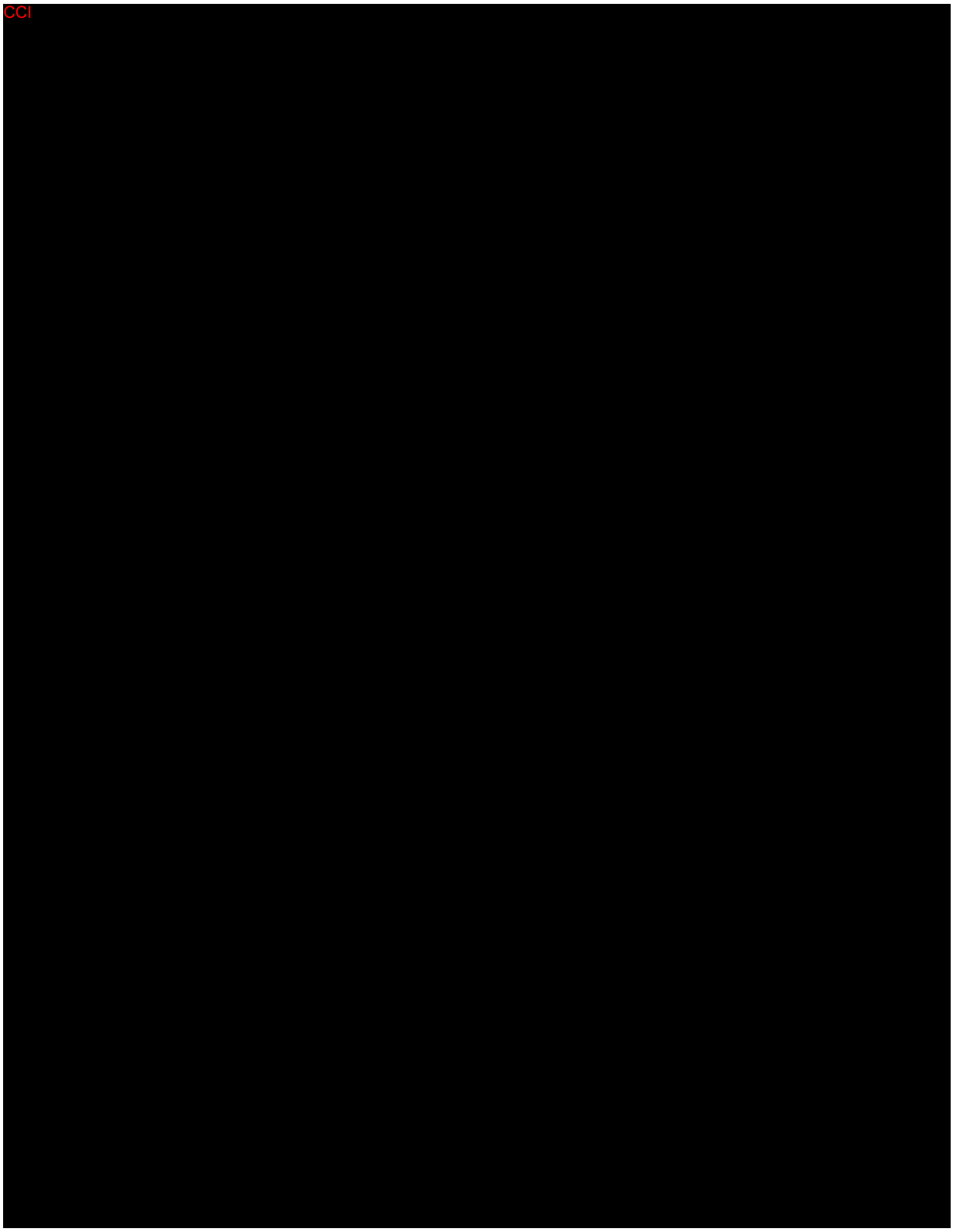
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10.7 Appendix 7: Collection and Management of Specimens for Future Biomedical Research

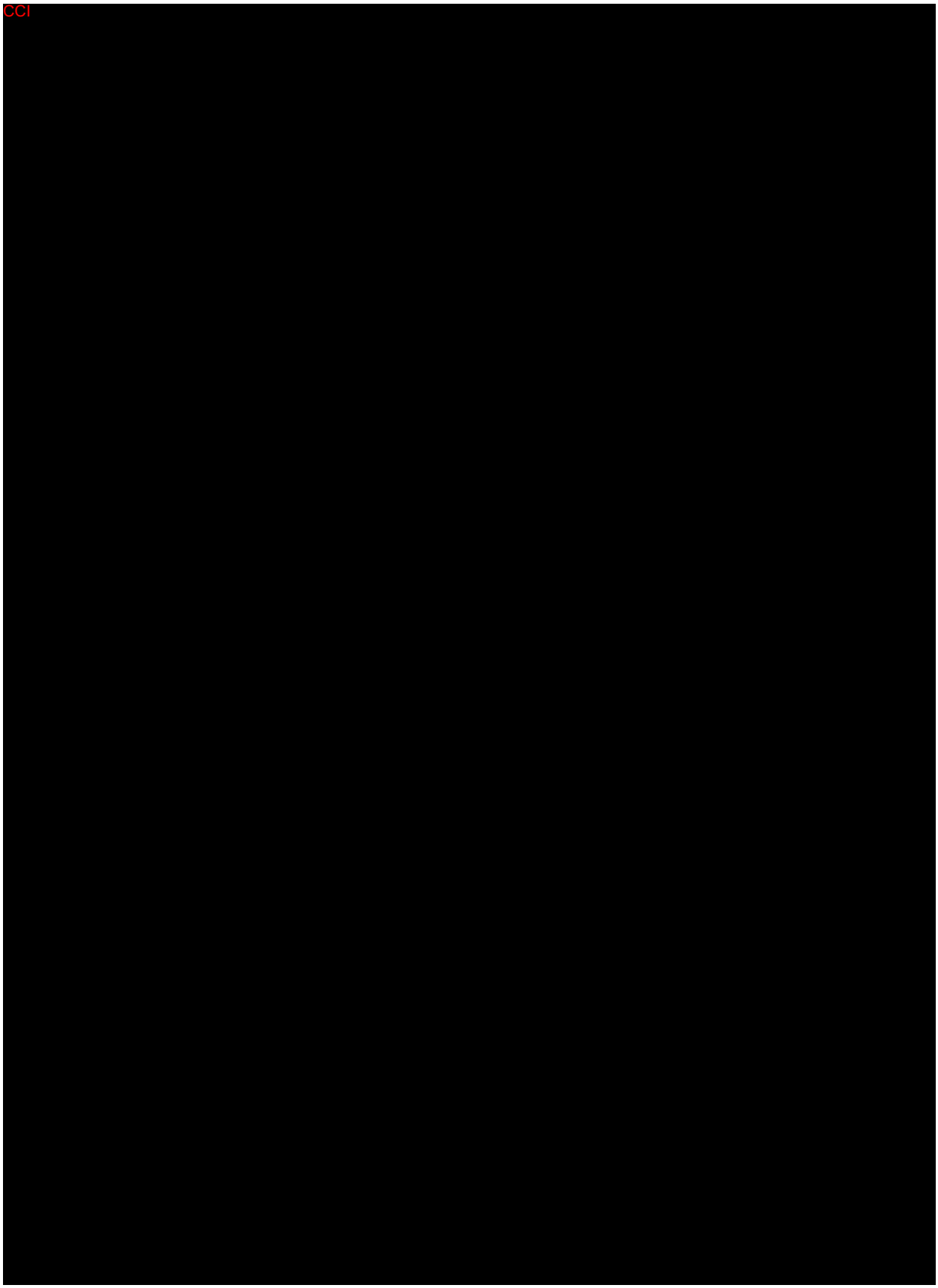
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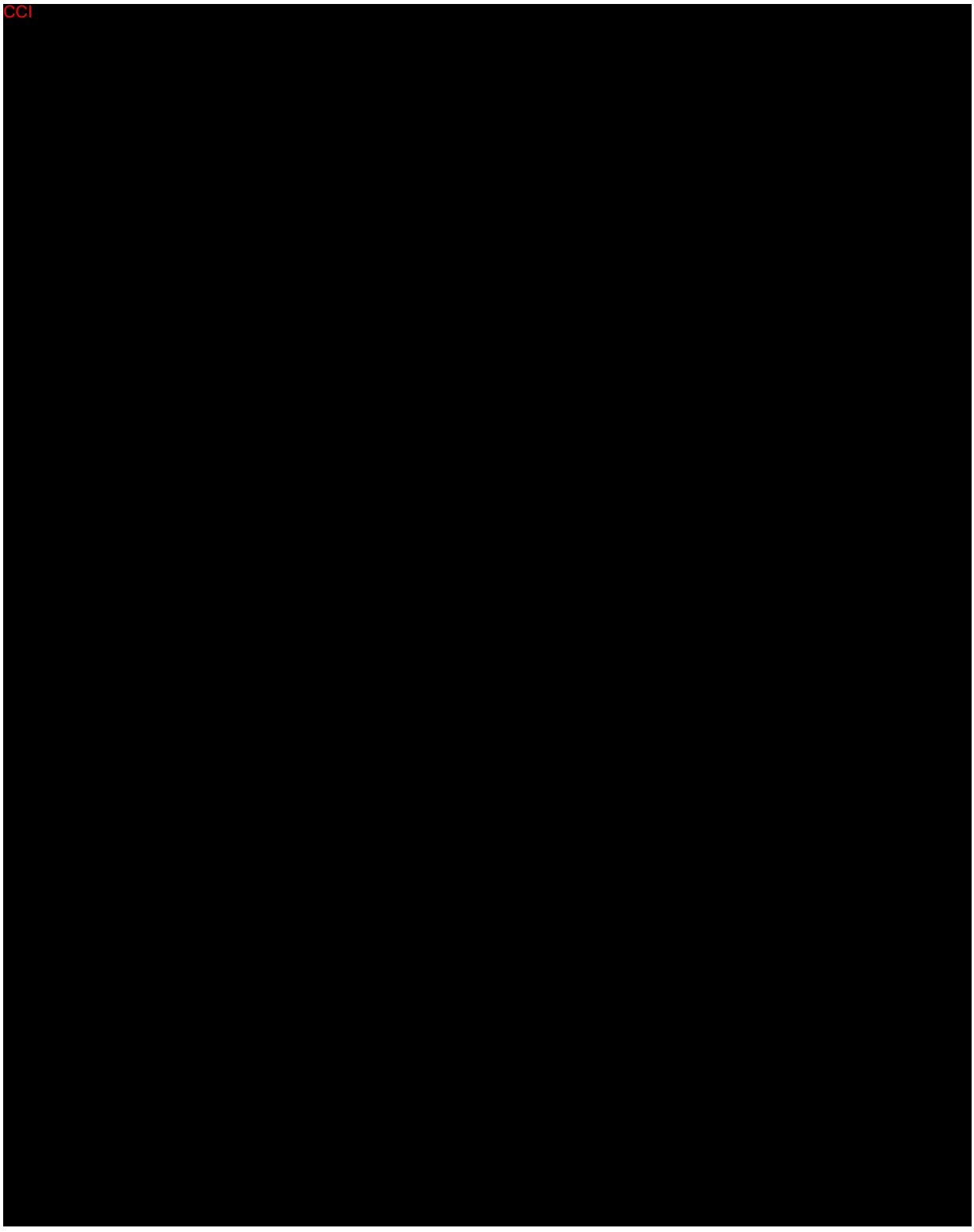
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10.8 Appendix 8: Country-specific Requirements

There are no country-specific requirements for Substudy 2.

10.9 Appendix 9: Description of the iRECIST Process for Assessment of Disease Progression

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 to guide decisions about changes in management.

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 radiological disease progression by RECIST 1.1, the investigator will decide whether to continue a participant on study intervention until repeat scans 4 to 8 weeks later are obtained, as described in Section 8.2.1.5.

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 ≥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 Scans

On the confirmatory scans, 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 disease progression 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 disease progression threshold (by RECIST 1.1)

Additional scans for confirmation are to be scheduled 4 to 8 weeks from the scans on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan 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 disease progression 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 Following the Confirmatory Scan

If repeat scans do not confirm disease progression, and the participant continues to be clinically stable, study intervention is to continue. The regular scan schedule is to be followed. If disease progression is confirmed, participants may be discontinued from study intervention.

NOTE: If a participant has confirmed radiographic progression (iCPD) and clinically meaningful benefit, study intervention may be continued after consultation with the Sponsor. If study intervention is continued, tumor scans are to be performed following the intervals as outlined in Section 1.3.

Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (ie, after iSD/iPR/iCR), another instance of progression (another iUPD) is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the disease progression threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- 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 Scan above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process on the subsequent iUPD is identical to the iUPD confirmation process for the initial disease progression, with one exception, which can occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number) leading to the second iUPD. If new lesion worsening has not resolved at the confirmatory scan 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 new or worsening cause of progression indicates iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APaT	All-Participants-as-Treated
aPTT/PTT	activated partial thromboplastin time/ partial thromboplastin time
AST	aspartate aminotransferase
ATD	accelerated titration design
AUC	area under the curve
BICR	Blinded Independent Central Review
BOR	best overall response
CBC	complete blood count
CI	confidence interval
COPD	chronic obstructive pulmonary disorder
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
DC	discontinuation
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOT	end of treatment
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FIH	first-in-human
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GEP	gene expression profile
GLP	Good Laboratory Practice
GFR	glomerular filtration rate

Abbreviation	Expanded Term
GI	gastrointestinal
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HLA-G	human leukocyte antigen-G
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	confirmed progressive disease by iRECIST
iCR	complete response by iRECIST
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILT	immunoglobulin-like transcript
IMP	Investigational Medicinal Product
IND	Investigational New Drug application
INR	international normalized ratio
IO	Immune-oncology
iPR	partial response by iRECIST
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified RECIST 1.1 for Immune-based Therapeutics
IRT	interactive response technology
iSD	stable disease by iRECIST
IV	intravenous
IVD	in vitro diagnostic
IUD	intrauterine device
iUPD	unconfirmed progressive disease by iRECIST
IUS	intrauterine hormone-releasing system
KN	Keynote
mAb	monoclonal antibody
MDSC	myeloid-derived suppressor cells
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
mRNA	messenger RNA
mTPI	modified toxicity probability interval
NIMP	Non-Investigational Medicinal Product
NOAEL	no-observed adverse effect level
NSAE	Nonserious Adverse Event
NSAID	nonsteroidal anti-inflammatory
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell(s)
PD	progressive disease
PD-1	programmed cell death 1
PD-1/L1	PD-1/PD-L1

Abbreviation	Expanded Term
PD-L1	programmed cell death 1 ligand 1
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic
po	per os; oral
PR	partial response
PT	prothrombin time
Q3W	every 3 weeks
RBC	red blood cell
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
ROS-1	c-ros oncogene 1
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SIM	Site Imaging Manual
SoA	Schedule of Activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine
T4	thyroxine
TBD	to be determined
TPS	Tumor Proportion Score
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WOCBP	woman/women of childbearing potential

11 REFERENCES

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