Official Protocol Title:	A Phase 2, Multicenter, Multi Arm, Study to Evaluate MK1308A (Co-formulated quavonlimab (MK1308)/ pembrolizumab) Versus Other Treatments in Participants with Microsatellite Instability-High (MSI-H) or Mismatch Repair
NCT number:	NCT04895722
Document Date:	28-Apr-2025

TITLE PAGE

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 2, Multicenter, Multi Arm, Study to Evaluate MK-1308A (Co-formulated quavonlimab (MK-1308)/pembrolizumab) Versus Other Treatments in Participants with Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Cancer: (MK-1308A-008)

Protocol Number: 008-05

Compound Number: MK-1308A

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT04895722
EU CT	2022-502100-70
EudraCT	2020-005114-18
JRCT	Not applicable
WHO/UTN	U1111-1283-2434
IND	155571

Approval Date: 28 April 2025

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	28-APR-2025	The purpose of this amendment is to provide details about study procedures and required follow-up upon closure of the MK-4280A, MK-7684A, and MK-4830+pembrolizumab arms and discontinuation of those programs.
Amendment 04	26-OCT-2023	The purpose of this amendment is to implement a change in strategy to provide guidance in the event a treatment arm closes.
Amendment 03	22-AUG-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Additional minor changes were also made throughout the protocol.
Amendment 02	21-JAN-2022	To clarify the occurrence of Day 22 visits in each cycle for Cohort B participants being treated on a Q6W schedule and address typographical errors/omissions.
Amendment 01	03-DEC-2021	To implement study design changes including expanding the treatment arms for Cohort B and removal of Cohort C, incorporate the changes from Protocol Clarification Letters dated 29-MAR-2021 and 10-MAY-2021, 17-JUN-2021, update the dose modification and toxicity management guidelines for irAEs and address typographical errors.
Original Protocol	22-FEB-2021	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendment:

The purpose of this amendment is to provide details about study procedures and required follow-up upon closure of the MK-4280A, MK-7684A, and MK-4830+pembrolizumab arms and discontinuation of those programs.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 4.1, Overall Design	Added text to describe study intervention information and references to Sections 6 and 8 for follow-up and Second Course treatment information for participants in closed arms.	To provide details about study procedures and required follow-up upon closure of the MK-4280A, MK-7684A, and MK-4830+ pembrolizumab arms and discontinuation of those programs.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Throughout	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other changes and their reasons are included for completeness.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.
Title Page	Regulatory Agency Identifying Number(s): Added the NCT number.	To incorporate newly available information.
	Regulatory Agency Identifying Number(s): Added the WHO/UTN number.	See rationale for Title Page (incorporation of newly available information).
Section 1.1, Synopsis	Indication: Updated to colorectal cancer stage IV.	To align with MedDRA terminology.
	Intervention Groups and Duration: Updated description of use for all study interventions.	To align with descriptions in Table 5.
	Intervention Groups and Duration: Added pembrolizumab row to the study interventions table for participants who received Q3W dosing in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Intervention Groups and Duration: Added text in footnotes to describe study intervention information for participants in closed arms and reasons for arm closures.	See rationale for Section 4.1 under primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
	Duration of Participation: Added text to describe that BICR verification for Second Course eligibility is only required for participants in open arms.	See rationale for Section 4.1 under primary reason for amendment.
	Duration of Participation: Added text to describe Second Course and posttreatment follow-up information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 1.2, Schema	Footnote e: Deleted text describing enrollment closure of the MK-4830+pembrolizumab arm.	Text is redundant with Section 6.1.1.1.
	Footnotes: Added note to refer to Sections 6.1.1 for study intervention information and Section 8.11.4 for posttreatment follow-up information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 1.3, Schedule of Activities	Added text to summarize information regarding procedures/assessments for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 1.3.2, Cohort B	Study Medication Administration: Added note to refer to Section 6.1.1.1 for study intervention information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Progression and Subsequent Antineoplastic Therapy Status: Added note to describe that this is not required for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Tumor Scans: Added note to refer to Section 8.2.1 for imaging information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Survival Status: Added note to describe that this is not required for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	EQ-5D-5L EORTC QLQ-C30: Added note to describe that PROs will no longer be collected for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	AE/SAE review: Added note to refer to Section 8.3 for safety monitoring information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Blood collection for Serum PK: Added note to describe that PK samples will no longer be collected for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Blood Collection for ADA: Added note to describe that ADA samples will no longer be collected for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Whole Blood Sample for MSI DNA Analysis: Added note to describe that biomarker samples will no longer be collected for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Blood for ctDNA Analysis: Added note to describe that biomarker samples will no longer be collected for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.3, Second Course Treatment	Study Intervention Administration: Added note to refer to Section 6.1.1.2 for Second Course treatment information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Progression and Subsequent Antineoplastic Therapy Status: Added note to describe that this is not required for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Tumor Scans: Added note to refer to Section 8.2.1 for imaging information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Survival Status: Added note to describe that this is not required for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	AE/SAE review: Added note to refer to Section 8.3 for safety monitoring information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Blood for ctDNA Analysis: Added note to describe that biomarker samples will no longer be collected for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 2.3, Benefit/Risk Assessment	Added brief summaries of the decision and previous closure to enrollment of the MK-4830+pembrolizumab arm, of new data from other MK-7684A clinical studies and the decision to discontinue the MK-7684A arm, and of the decision to discontinue the MK-4280A arm.	See rationale for Section 4.1 under primary reason for amendment.
Section 4.1, Overall Design	Added text to describe that survival follow-up is only required for participants in open arms.	See rationale for Section 4.1 under primary reason for amendment.
	Added text to describe that BICR verification during posttreatment follow-up for disease status is only required for participants in open arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 4.3.2, Justification of Pembrolizumab Dose	Added description of the dosage of pembrolizumab for participants who received Q3W dosing in closed arms and who elect to transition to pembrolizumab monotherapy.	See rationale for Section 4.1 under primary reason for amendment.
Section 4.4, Beginning and End-of-Study Definition	Replaced examples of situations that would be considered lost to follow up with a reference to Section 7.3.	Text is redundant with Section 7.3.
	Added text to describe the duration of the study.	To align with EU CTR 536/2014.

Section Number and Name	Description of Change	Brief Rationale
Section 6.1, Study Intervention(s) Administered	Table 5: Updated descriptions of dose formulations for all study interventions.	To align with ISO standards.
	Table 5: Added pembrolizumab row to the study interventions table for participants who received Q3W dosing in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Added new level 3 heading (Section 6.1.1, Treatment).	To group the Initial Treatment or First Course and Second Course subsections.
	Sections 6.1.1 and 6.1.2 were renumbered to Sections 6.1.1.1 and 6.1.1.2, respectively.	To account for the addition of Section 6.1.1.
Section 6.1.1.1, Initial Treatment or First Course	Added text to describe study intervention information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 6.1.1.2, Second Course	Updated existing Second Course text and added text to describe Second Course treatment information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 6.4, Study Intervention Compliance	Updated text regarding verification of study intervention administration.	To align with regulatory requirements.
Section 7.1, Discontinuation of Study Intervention	Added text to refer to Section 8.11.4 for posttreatment follow-up information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.1.10, Discontinuation and Withdrawal	Added text to refer to Section 8.11.4 for posttreatment follow-up information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.2.1, Tumor Imaging and Assessment of Disease	Added medical photography as an example of cross-sectional imaging.	For completeness.
	Added text to describe imaging information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.2.1.2, Tumor Scans During the Study	Added text to describe that BICR verification of disease progression is only required for participants in open arms.	See rationale for Section 4.1 under primary reason for amendment.
	Added text to refer to Section 8.2.1 for imaging information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.2.1.3, End-of-treatment and Follow-up Tumor Scans	Added text to refer to Section 8.11.4 for posttreatment follow-up information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.2.1.4, Second Course (Retreatment) Tumor Scans	Added text to describe that BICR verification for Second Course eligibility is only required for participants in open arms.	See rationale for Section 4.1 under primary reason for amendment.
	Added text to refer to Section 8.2.1 for imaging information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
Section 8.2.1.5, RECIST 1.1 Assessment of Disease	Added text to describe that BICR verification of disease progression is only required for participants in open arms.	See rationale for Section 4.1 under primary reason for amendment.
	Added text to refer to Section 8.2.1 for imaging information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.2.2, Patient-reported Outcomes	Added text to describe PRO collection information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.3, Safety Assessments	Added text to describe safety monitoring information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Replaced the time period for collection of pregnancy and exposure during breastfeeding with a reference to Section 5.1.	Text is redundant with Section 5.1.
	Deleted text regarding reporting pregnancy at the time of initial screening.	Text is redundant with contents of Table 8.
	Table 8: Updated periods and duration for potential DILI events meeting biochemical criteria of Hy's Law.	To maintain continued regulatory reporting compliance in alignment with new Health Authority DILI reporting requirements.
Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information	Added potential DILI events meeting biochemical criteria of Hy's Law to reportable events.	See rationale for Section 8.4.1 (DILI reporting).
Section 8.4.4, Regulatory Reporting Requirements for SAE	Added text to describe SUSAR reporting in EEA countries.	See rationale for Section 4.4 (EU CTR 536/2014 alignment).
Section 8.4.7, Events of Clinical Interest	Updated ECI to potential DILI meeting biochemical criteria of Hy's Law, with associated reporting requirements.	See rationale for Section 8.4.1 (DILI reporting).
Section 8.6, Pharmacokinetics	Added text to describe PK/ADA sample collection information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.8, Biomarkers	Added text to describe biomarker sample collection information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.10, Medical Resource Utilization and Health Economics	Added text to describe medical resource utilization and health economics collection information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
Section 8.11, Visit Requirements	Added text to refer to Section 6.1.1 for study intervention and Section 8 for efficacy, PRO, safety, sample collection, and posttreatment follow-up information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
	Added new level 3 heading (Section 8.11.4, Posttreatment Visits).	To group the Safety Follow-up Visit, Efficacy Follow-up Visits, and Survival Follow-up Contacts subsections.
	Sections 8.11.3.1, 8.11.3.2, 8.11.3.3, and 8.11.4 were renumbered to Sections 8.11.4.1, 8.11.4.2, 8.11.4.3, and 8.11.5, respectively.	To account for the addition of Section 8.11.4.
Section 8.11.4, Posttreatment Visits	Added text to describe posttreatment follow-up information for participants in closed arms.	See rationale for Section 4.1 under primary reason for amendment.
Section 8.11.5, Vital Status	Added text to describe vital status collection for participants who have either withdrawn consent or are lost to follow-up.	To ensure that vital status information is collected in accordance with local regulations.
Section 9, Statistical Analysis Plan	Added text to describe future analysis plans.	To align with the latest analysis strategy.
Section 10.1.1, Code of Conduct for Interventional Clinical Trials	Updated code of conduct.	To align with ICH E6(R3).
Section 10.1.3, Data Protection	Added text to describe information about EU-approved Binding Corporate Rules.	See rationale for Section 4.4 (EU CTR 536/2014 alignment).
Section 10.1.6, Compliance with Study Registration and Results Posting Requirements	Added text to describe that a summary of the study results will be submitted in compliance with the EU CTR.	See rationale for Section 4.4 (EU CTR 536/2014 alignment).
Section 10.1.7, Compliance with Law, Audit, and Debarment	Added text to describe serious breach reporting requirements.	See rationale for Section 4.4 (EU CTR 536/2014 alignment).
Section 10.1.8, Data Quality Assurance	Added the EU CTR retention period for records and documents.	See rationale for Section 4.4 (EU CTR 536/2014 alignment).
Section 10.3.3, Definition of SAE	Added potential DILI events meeting biochemical criteria of Hy's Law to definition of SAE.	See rationale for Section 8.4.1 (DILI reporting).

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, Multicenter, Multi Arm, Study to Evaluate MK-1308A (Co-formulated quavonlimab (MK-1308)/pembrolizumab) Versus Other Treatments in Participants with Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Cancer: (MK-1308A-008)

Short Title: A Multi Arm Study in Participants with MSI-High Metastatic Colorectal Cancer

Acronym: KEYSTEP-008

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male and female participants who are at least 18 years of age, with mismatch repair deficient or microsatellite instability-high Stage IV colorectal cancer who have measurable disease per RECIST 1.1 by Blinded Independent Central Review, and who are either chemotherapy refractory (Cohort A), or have received no prior lines of systemic therapy for Stage IV disease (Cohort B).

Primary Objectives	Primary Endpoints
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Objective Response Rate per RECIST 1.1 as assessed by Blinded Independent Central Review	Objective Response: Complete Response or Partial Response
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Objective Response Rate per RECIST 1.1 as assessed by Blinded Independent Central Review	Objective Response: Complete Response or Partial Response

Secondary Objectives	Secondary Endpoints
Objective (Cohorts A and B): To evaluate Duration of Response per RECIST 1.1 as assessed by Blinded Independent Central Review	The time from first documented evidence of Complete Response or Partial Response until disease progression or death due to any cause, whichever occurs first
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Progression-Free Survival per RECIST 1.1 as assessed by Blinded Independent Central Review	Progression-Free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Progression-Free Survival per RECIST 1.1 as assessed by Blinded Independent Central Review	Progression-Free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Progression-Free Survival per RECIST 1.1 as assessed by the investigator	Progression-Free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Progression-Free Survival per RECIST 1.1 as assessed by the investigator	Progression-Free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Objective Response Rate per RECIST 1.1 as assessed by the investigator	Objective Response: Complete Response or Partial Response
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Objective Response Rate per RECIST 1.1 as assessed by the investigator	Objective Response: Complete Response or Partial Response

Objective (Cohort A and B): To evaluate Duration of Response per RECIST 1.1 as assessed by the investigator	The time from first documented evidence of Complete Response or Partial Response until disease progression or death due to any cause, whichever occurs first
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Overall Survival	Overall Survival: The time from randomization to death due to any cause
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Overall Survival	Overall Survival: The time from randomization to death due to any cause
Objective (Cohort A): To evaluate the safety and tolerability of MK-1308A compared to pembrolizumab monotherapy	Adverse Events Study intervention discontinuation due to Adverse Events
Objective (Cohort B): To evaluate the safety and tolerability of MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and compared to pembrolizumab monotherapy	Adverse Events Study intervention discontinuation due to Adverse Events

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Colorectal cancer stage IV
Population	Participants with dMMR/MSI-H Stage IV CRC who are chemotherapy refractory (Cohort A) or who have received no prior lines of systemic therapy for Stage IV disease (Cohort B)
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control without placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 60 months 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:

Approximately 320 participants will be allocated to complete the study as described in Section 9.9.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Cohorts A and B: Pembrolizumab monotherapy	Pembrolizumab	25 mg/mL	400 mg	IV Infusion	Q6W up to 17 doses	Comparator
Cohorts A and B: MK-1308A	MK-1308A	quavonlimab 25 mg + pembrolizumab 400 mg/ 17.5 mL vial	25 mg/ 400 mg	IV Infusion	Q6W up to 17 doses	Test Product
Cohort B: MK-4280A	MK-4280A	20 mg/mL favezelimab + 5 mg/mL pembrolizumab for a total of 25 mg/mL	800 mg MK-4280 + 200 mg MK-3475	IV Infusion	Q3W up to 35 doses	Test Product
Cohort B: MK-7684A	MK-7684A	vibostolimab 10 mg/mL + pembrolizumab 10 mg/mL	200 mg MK-7684 + 200 mg MK-3475	IV Infusion	Q3W up to 35 doses	Test Product
Cohort B: MK-4830 + Pembro-lizumab	MK-4830 + Pembro-lizumab	MK-4830 50 mg/mL + pembrolizumab 25 mg/mL	800 mg MK-4830 + 200 mg MK-3475	IV Infusion	Q3W up to 35 doses	Test Product
Cohort B: Participants who received Q3W dosing in closed arms	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Q3W up to a total of 35 doses including doses received as part of closed arm	Comparator

IV=intravenous; Q3W= every 3 weeks; Q6W=every 6 weeks.

MK-1308A refers to coformulated quavonlimab/pembrolizumab.

MK-4280A refers to coformulated favezelimab/pembrolizumab. As of the Investigator Letter dated 16-DEC-2024, participants who were receiving MK-4280A were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy. This decision was made after a thorough evaluation of data from the favezelimab clinical program and is not based on any concerns about the safety of this fixed-dose combination.

MK-7684A refers to coformulated vibostolimab/pembrolizumab. As of the Investigator Letter dated 16-DEC-2024 and as allowed per protocol text inserted in Amendment 04 regarding the possibility of closing study arms, participants who were receiving MK-7684A were discontinued from that study therapy and offered the option to transition to pembrolizumab monotherapy. This decision was based on an unfavorable risk-benefit balance and not on any concerns about the safety of this fixed-dose combination.

MK-4830+pembrolizumab refers to combination MK-4830 plus pembrolizumab (this arm was closed to enrollment on 22-SEP-2023 with CCI participants randomized). As per the Investigator Letter dated 25-SEP-2023, participants who were receiving MK-4830+pembrolizumab were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy. This decision was based on a lack of clinical efficacy of MK-4830 in combination with pembrolizumab in several tumor types across all MK-4830-related studies and not on any concerns about the safety of this combination.

Total Number of Intervention Groups/Arms	7 intervention groups
Duration of Participation	Each participant will participate in the study for approximately 3 years from the time the participant provides documented informed consent through the final protocol-specified contact. After Screening, each participant will be receiving assigned intervention for up to approximately 2 years. After a screening phase of 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants who require interruption of a coformulation or combination treatment for toxicity, who then recover, may either resume the same coformulation or combination treatment or may initiate pembrolizumab monotherapy at the discretion of the investigator and with Sponsor consultation. In the event of a study arm being closed, the Sponsor may elect to require de-escalation to pembrolizumab monotherapy or may offer investigators the option of continuing the assigned study treatment to participants who are receiving clinical benefit. Participants who complete study intervention after receiving their full assigned treatment, and participants who attain a complete response and stop study intervention may be eligible for a second treatment course (approximately 1 year) upon experiencing disease progression, as assessed by the site and, for participants in open arms, verified by BICR (for participants in open arms). For participants in closed arms, Second Course will be offered with pembrolizumab monotherapy only. After the end-of-treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy.

	Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. Participants in closed arms who complete study treatment (including Second Course, if applicable) or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. All participants will be followed for overall survival until death, withdrawal of consent, or end of the study. For participants in closed arms, there will be no follow up for survival status.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Steering Committee	No

Supporting Documentation and Operational Considerations are outlined in Appendix 1.

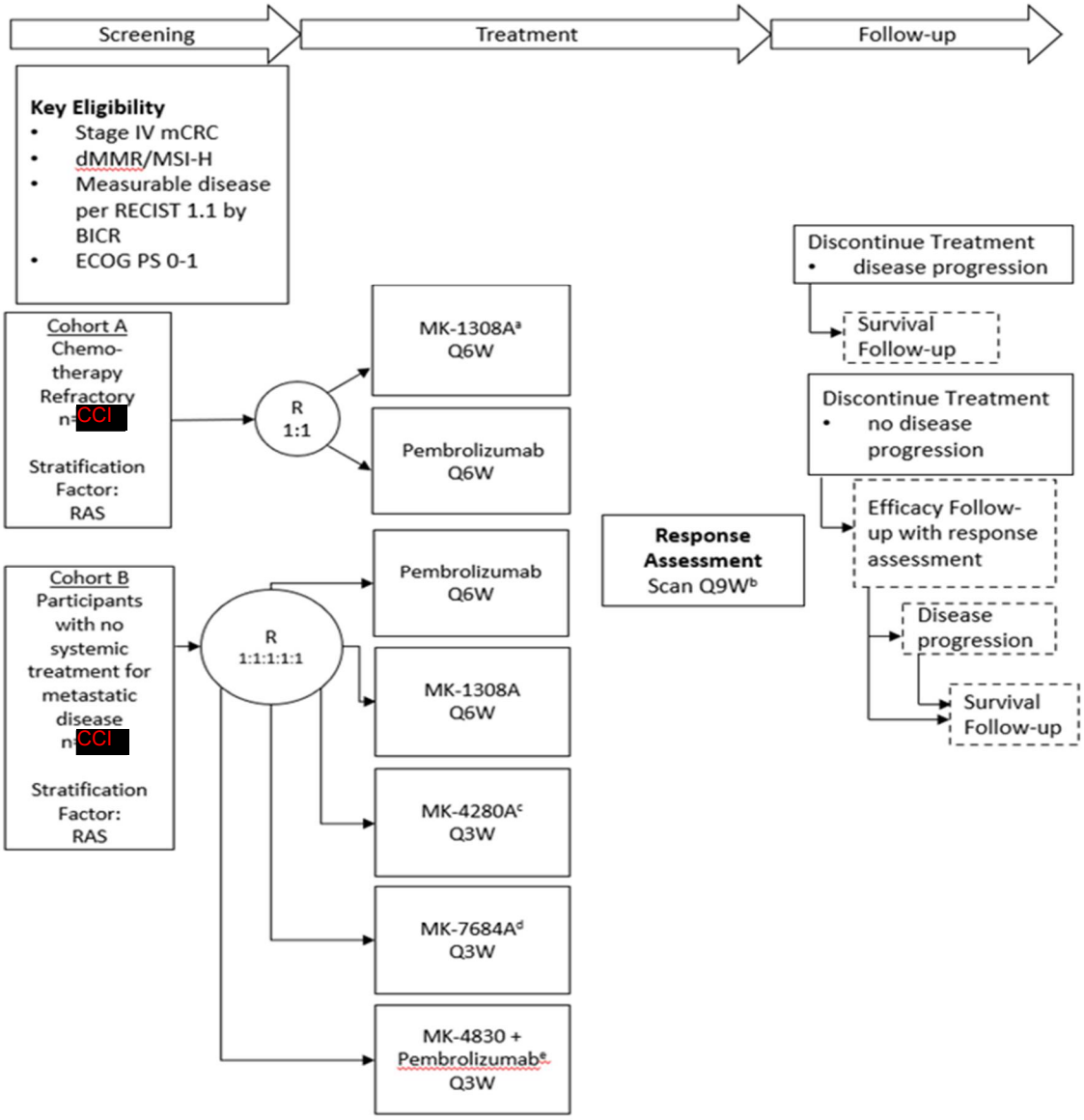
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram



1L=first line of therapy; BICR=blinded independent central review; dMMR=mismatch repair deficient; ECOG PS=Eastern Cooperative Oncology Group Performance Status; mCRC=metastatic colorectal cancer; MSI-H=microsatellite instability-high; PD-1=programmed cell death 1 protein; Q3W= every 3 weeks; Q6W=every 6 weeks; Q9W=every 9 weeks; R=randomization; RECIST=Response Evaluation Criteria In Solid Tumors.

[a] Coformulated quavonlimab/pembrolizumab (quavonlimab 25 mg with pembrolizumab 400 mg).
[b] Per RECIST 1.1 by BICR.
[c] Coformulated favezelimab/pembrolizumab (favezelimab 800 mg with pembrolizumab 200 mg).
[d] Coformulated vibostolimab/pembrolizumab (vibostolimab 200 mg with pembrolizumab 200 mg).
[e] Combination MK-4830+pembrolizumab (MK-4830 800 mg + pembrolizumab 200 mg).

Note: Refer to Section 6.1.1 for study intervention information and Section 8.11.4 for posttreatment follow-up information for participants in closed arms.

1.3 Schedule of Activities

At implementation of Amendment 05, the following treatment arms are considered closed: Cohort B: MK-4280A, Cohort B: MK-7684A, and Cohort B: MK-4830+pembrolizumab.

As of the Investigator Letter dated 16-DEC-2024, participants who were receiving MK-4280A were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy, and participants who were receiving MK-7684A were discontinued from that study therapy and offered the option to transition to pembrolizumab monotherapy.

As per the Investigator Letter dated 25-SEP-2023, the MK-4830+pembrolizumab arm was closed to enrollment; all ongoing participants were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy.

Refer to Section 8.2.1 for imaging information and Section 8.3 for safety monitoring information for participants in closed arms.

The following procedures/assessments are not required for participants in closed arms:

- PRO assessments
- PK/ADA sample collection
- Biomarker sample collection
- Follow-up for progression, subsequent antineoplastic therapy status, and survival

Refer to Section 6.1.1.2 for Second Course treatment information for participants in closed arms.

1.3.1 Cohort A

Table 1 Study Schedule of Activities – Cohort A

Study Period:	**Screening**	**Intervention (Q6W)**					**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2		Cycles 3 to 17		Safety FU	Efficacy FU	Survival FU	
Cycle Day	Up to 28 days prior to first dose	1	22	1	22	1	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Administrative Procedures											
Informed Consent	X										If the investigator plans to treat beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent (see Section 8.1.1.1).
Informed Consent for Future Biomedical Research (optional)	X										To be obtained after consenting to the main study.
Inclusion/Exclusion Criteria	X	X									
Participant Identification Card	X	X									Add the allocation number at the time of allocation.
Demographics and Medical History	X										
Oncologic Medical History (oncology disease status, MSI/MMR status, and prior oncology treatment history including surgery)	X										

Study Period:	**Screening**	**Intervention (Q6W)**					**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2		Cycles 3 to 17		Safety FU	Efficacy FU	Survival FU	
Cycle Day	Up to 28 days prior to first dose	1	22	1	22	1	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
CCI [redacted]											
Prior/Concomitant Medication Review	X	X	X	X	X*	X	X	X			Record concomitant medications beyond 30 days after treatment discontinuation if related to an SAE or ECI. *May be conducted by telephone or video at the discretion of the investigator or qualified designee.
Randomization (via IRT)		X									To be completed after confirmation of eligibility.
Study Medication Administration		X		X		X					
Progression and Subsequent Antineoplastic Therapy Status							X	X	X	X	All progression events and anticancer therapy will be recorded during follow-up until time of death or termination of survival follow-up. If a clinical visit is not feasible, follow-up information may be obtained by other means such as telephone or email.

Study Period:	**Screening**	**Intervention (Q6W)**					**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2		Cycles 3 to 17		Safety FU	Efficacy FU	Survival FU	
Cycle Day	Up to 28 days prior to first dose	1	22	1	22	1	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Efficacy Assessments											
Tumor Scans (CT/MRI Chest, Abdomen, and Pelvis)	X	←				→			X		All imaging assessments should follow calendar days regardless of cycle delays. Tumor scans should be performed Q9W (63 ±7 days), from the date of allocation or more frequently if clinically indicated.
Survival Status	X	←								X	Survival Follow-up phase begins after investigator determined disease progression or the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.
Patient-reported Outcomes											
EQ-5D-5L EORTC QLQ-C30		X		X		X*	X	X			Perform PROs in the order listed in Column 1 of the SoA. Every effort should be made to administer PROs before drug administration, AE evaluation, and disease status notification. *ePRO collection is required at C3, C4, then every other cycle (ie, C6, C8, etc) until EOT or treatment discontinuation, whichever occurs first, and at the post treatment Safety Follow-up Visit. A visit window of ±7 days will apply to every PRO visit assessment after C1.

Study Period:	**Screening**	**Intervention (Q6W)**					**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2		Cycles 3 to 17		Safety FU	Efficacy FU	Survival FU	
Cycle Day	Up to 28 days prior to first dose	1	22	1	22	1	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Safety Assessments											
Full Physical Examination	X						X				
Height	X										
Weight	X	X		X		X	X	X			
Directed Physical Examination		X	X	X		X		X	X*		*May be conducted by telephone or video at the discretion of the investigator or qualified designee.
Vital Signs (temperature, HR, RR, DBP, SBP)	X	X	X	X		X	X	X			BP and pulse rate will be measured after the participant has been resting for 5 minutes. Include pulse oximetry (SpO2) if locally required.
12-lead ECG	X					X*	X				*Repeat if clinically indicated.
ECOG Performance Status	X	X		X		X	X	X			Must be performed within 3 days of C1D1 treatment and before treatment at each cycle.
AE/SAE review	X	←									AEs monitored up to 30 days after last dose. SAEs monitored up to 90 days and pregnancy monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner. On C2D22, may be conducted by telephone or video at the discretion of the investigator or qualified designee.

Study Period:	**Screening**	**Intervention (Q6W)**					**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2		Cycles 3 to 17		Safety FU	Efficacy FU	Survival FU	
Cycle Day	Up to 28 days prior to first dose	1	22	1	22	1	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Laboratory Assessments											
Hematology/ Chemistry	X	X*		X		X	X	X			Collect predose. * Collect within 72 hours before first study intervention dose.
Urinalysis	X	X*		X*		X*	X	X			Collect within 72 hours before first study intervention dose. *As clinically indicated.
Serum or Urine Pregnancy test (WOCBP only)	X	X		X	X	X	X	X			WOCBP require a negative test prior to randomization. If more than 24 hours for a urine test or 72 hours for a serum test have elapsed prior to the first dose of study intervention, another pregnancy test is required. See additional country-specific requirements in Appendix 7.
PT/INR and aPTT/PTT (baseline only)	X										Additional testing to be conducted as clinically indicated.
HIV, HBsAg, HCV	X*										*Only if required by local health authority. See country-specific requirements in Appendix 7.

Study Period:	**Screening**	**Intervention (Q6W)**					**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2		Cycles 3 to 17		Safety FU	Efficacy FU	Survival FU	
Cycle Day	Up to 28 days prior to first dose	1	22	1	22	1	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Thyroid Function Tests (TSH, T3, T4), Cortisol, and ACTH**	X	X*	X	X		X	X	X			Free T3 and Free T4 are acceptable if total T3 and total T4 are unavailable. After Cycle 1, retrospective review of thyroid function, ACTH and cortisol testing results is allowed when the results are not available before dosing. *Collection is optional on C1D1. **ACTH testing is to be done as required per investigator's discretion
Serum Tumor Marker (CEA)	X	X		X		X	X		X		Dosing permitted prior to results of CEA being known.
PK/ADA/Biomarkers											
[redacted]											

Study Period:	Screening	Intervention (Q6W)					EOT	Posttreatment			Notes
Visit Number/Title:	Screening	Cycle 1		Cycle 2		Cycles 3 to 17		Safety FU	Efficacy FU	Survival FU	
Cycle Day	Up to 28 days prior to first dose	1	22	1	22	1	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
CCI											

ACTH=adrenocorticotropic hormone; ADA=antidrug antibodies; AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; BRAF=B-Raf gene; C=cycle; CEA=carcinoembryonic antigen; CT=computed tomography; (ct)DNA=(circulating tumor) deoxyribonucleic acid; D=day; DBP=diastolic blood pressure; DC=discontinuation; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end of treatment; (e)PRO=electronic patient-reported outcome; EQ-5D-5L=EuroQoL 5-dimension, 5-level scale; FU=follow-up; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; INR=international normalized ratio; IRT=interactive response technology; KRAS=Kirsten rat sarcoma viral oncogene homolog; MMR=mismatch repair; MRI=magnetic resonance imaging; MSI=microsatellite instability; NAb=neutralizing antibody; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q6W=every 6 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; RAS=genes that makes the proteins called KRAS, HRAS, and NRAS; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; SoA=schedule of activities; SpO2=oxygen saturation; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.2 Cohort B

Table 2 Study Schedule of Activities – Cohort B

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Administrative Procedures										
Informed Consent	X									If the investigator plans to treat beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent (see Section 8.1.1.1).
Informed Consent for Future Biomedical Research (optional)	X									To be obtained after consenting to the main study.
Inclusion/Exclusion Criteria	X	X								
Participant Identification Card	X	X								Add the allocation number at the time of allocation.
Demographics and Medical History	X									
Oncologic Medical History (oncology disease status, MSI/MMR status and prior oncology treatment history including surgery)	X									
RAS (KRAS and NRAS) and BRAF mutation status	X									Results must be obtained by the site before C1D1 allocation. Only perform if status is not already known. Perform per institutional standards.

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X			Record concomitant medications beyond 30 days after treatment discontinuation if related to an SAE or ECI.
Randomization (via IRT)		X								To be completed after confirmation of eligibility.
Study Medication Administration		X		X*						*Required every 6 weeks for participants randomized to the MK-1308A or pembrolizumab monotherapy arms and every 3 weeks for participants randomized to the MK-4280A, MK-7684A, or MK-4830+pembrolizumab arms. Refer to Section 6.1.1.1 for study intervention information for participants in closed arms.
Progression and Subsequent Antineoplastic Therapy Status						X	X	X	X	All progression events and anticancer therapy will be recorded during follow-up until time of death or termination of survival follow-up. If a clinical visit is not feasible, follow-up information may be obtained by other means such as telephone or email. Not required for participants in closed arms.

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Efficacy Assessments										
Tumor Scans (CT/MRI Chest, Abdomen, and Pelvis)	X	←			→			X		All imaging assessments should follow calendar days regardless of cycle delays. Tumor scans should be performed Q9W (±7 days), from the date of allocation or more frequently if clinically indicated. Refer to Section 8.2.1 for imaging information for participants in closed arms.
Survival Status	X	←							X	Survival follow-up begins after investigator determined disease progression or the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study. Not required for participants in closed arms.

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Patient-reported Outcomes										
CCI [redacted]										
Safety Assessments										
Full Physical Examination	X					X				
Height	X									
Weight	X	X	X	X	X	X	X			
Directed Physical Examination as clinically indicated		X	X	X	X		X	X*		*May be conducted by telephone or video at the discretion of the investigator or qualified designee.

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
Vital Signs (temperature, HR, RR, DBP, SBP)	X	X	X	X	X	X	X			BP and pulse rate will be measured after the participant has been resting for 5 minutes. Include pulse oximetry (SpO2) if locally required.
12-lead ECG	X		X*	X*	X*	X				*As clinically indicated.
ECOG Performance Status	X	X	X	X	X	X	X			Must be performed within 3 days of C1D1 treatment and before treatment at each cycle.
AE/SAE review	X	←						→		AEs monitored up to 30 days after last dose. SAEs monitored up to 90 days and pregnancy monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner. Refer to Section 8.3 for safety monitoring information for participants in closed arms.
Laboratory Assessments										
Hematology/Chemistry	X	X*	X	X	X	X	X			Collect Predose. *Collect within 72 hours before first study intervention dose.
Urinalysis	X	X*	X*	X*	X*	X*	X			*As clinically indicated Collect within 72 hours before first study intervention dose.
Serum or Urine Pregnancy test (WOCBP only)	X	X		X		X	X			WOCBP require a negative test prior to allocation. If more than 24 hours for a urine test or 72 hours for a serum test have elapsed prior to the first dose of study intervention, another pregnancy test is required. See country-specific requirements in Appendix 7.

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
PT/INR and aPTT/PTT (baseline only)	X									Additional testing to be conducted as clinically indicated.
HIV, HBsAg, HCV	X*									*Only if required by local health authority. See country-specific requirements in Appendix 7.
Thyroid Function Tests (TSH, T3, T4), Cortisol, and ACTH**	X		X	X		X	X			Free T3 and Free T4 are acceptable if total T3 and total T4 are unavailable. After C1, retrospective review of thyroid function, ACTH and cortisol testing results is allowed when the results are not available prior to dosing. **ACTH testing is to be done as required per investigator's discretion.
Serum Tumor Marker (CEA)	X	X	X	X		X		X		Dosing permitted prior to results of CEA being known.

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
CCI [redacted]										

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
CCI [redacted]										
Archival or Newly Obtained Tissue Collection	X									May use archival tissue sample obtained within 5 years of screening period.
CCI [redacted]										

Study Period:	**Screening**	**Intervention**				**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Screening	Cycle 1		Cycle 2 onwards*			Safety FU	Efficacy FU	Survival FU	*Cycles 2 to 17 for Q6W schedule; Cycle 2 to 35 for Q3W schedule.
Cycle Day	Up to 28 days prior to first dose	1	Day 22 (Q6W regimens only)	1	Day 22 (Q6W regimens only)	DC	30 days after last dose			
Scheduling Window (days):	-28 to -1	+3	±3	±3	±3		+7	Q9W ±7	Q12W ±14	
CCI										

ACTH=adrenocorticotropic hormone; ADA=antidrug antibodies; AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; BRAF=B-Raf gene; C=cycle; CEA=carcinoembryonic antigen; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DBP=diastolic blood pressure; DC=discontinuation; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end of treatment; ePRO=electronic patient-reported outcome; EQ-5D-5L=EuroQoL 5-dimension, 5- level scale; FU=follow-up; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; INR=international normalized ratio; IRT=interactive response technology; KRAS=Kirsten rat sarcoma viral oncogene homolog; MMR=mismatch repair; MRI=magnetic resonance imaging; MSI=microsatellite instability; NAb=neutralizing antibody; PK=pharmacokinetic; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q6W=every 6 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; RAS=genes that makes the proteins called KRAS, HRAS, and NRAS; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; SoA=schedule of activities; SpO2=oxygen saturation; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.3 Second Course Treatment

Table 3 Study Schedule of Activities – Second Course Treatment

Study Period:	**Intervention**		**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Cycle 1	Cycles 2 to 17 (2 to 9 for Q6W schedule)		Safety FU	Efficacy FU	Survival FU	
Cycle Day	1	1	DC	30 days after last dose			
Scheduling Window (days):	±3	±3		+7	Q9W ±7	Q12W ±14	
Administrative Procedures							
Eligibility Criteria	X						
Concomitant Medication Review	X	X	X	X			Record concomitant medications beyond 30 days after treatment discontinuation if related to an SAE or ECI.
Study Intervention Administration	X	X*					*Required every 6 weeks for participants randomized to the MK-1308A or pembrolizumab monotherapy arms and every 3 weeks for participants randomized to the MK-4280A, MK-7684A, or MK-4830+pembrolizumab arms. Refer to Section 6.1.1.2 for Second Course treatment information for participants in closed arms.
Progression and Subsequent Antineoplastic Therapy Status			X	X	X	X	All progression events and anticancer therapy will be recorded during follow-up until time of death or termination of survival follow-up. If a clinical visit is not feasible, follow-up information may be obtained by other means such as telephone or email. Not required for participants in closed arms.

Study Period:	**Intervention**		**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Cycle 1	Cycles 2 to 17 (2 to 9 for Q6W schedule)		Safety FU	Efficacy FU	Survival FU	
Cycle Day	1	1	DC	30 days after last dose			
Scheduling Window (days):	±3	±3		+7	Q9W ±7	Q12W ±14	
Efficacy Assessments							
Tumor Scans (CT/MRI Chest, Abdomen, and Pelvis)	←	→			X		All imaging assessments should follow calendar days regardless of cycle delays. Tumor scans should be performed within 28 days before restarting study treatment and continue to be performed Q9W (63 ± 7 days) from C1D1 or more frequently if clinically indicated. Refer to Section 8.2.1 for imaging information for participants in closed arms.
Survival Status	←	→				X	Survival follow-up begins after investigator determined disease progression or the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study. Not required for participants in closed arms.
Safety Assessments							
Full physical examination			X				
Height	X						
Weight	X	X	X	X			
Directed Physical Examination as clinically indicated	X	X		X	X*		*May be conducted by telephone or video at the discretion of the investigator or qualified designee.
Vital Signs (temperature, HR, RR, DBP, SBP)	X	X	X	X			BP and pulse rate will be measured after the participant has been resting for 5 minutes. Include pulse oximetry (SpO2) if locally required.

Study Period:	**Intervention**		**EOT**	**Posttreatment**			**Notes**
Visit Number/Title:	Cycle 1	Cycles 2 to 17 (2 to 9 for Q6W schedule)		Safety FU	Efficacy FU	Survival FU	
Cycle Day	1	1	DC	30 days after last dose			
Scheduling Window (days):	±3	±3		+7	Q9W ±7	Q12W ±14	
12-lead ECG	X	X*	X				*As clinically indicated.
ECOG Performance Status	X	X	X	X			Must be performed before treatment at each cycle.
AE/SAE review	◄———	———	———►				AEs monitored up to 30 days after last dose. SAEs monitored up to 90 days and pregnancy monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner. Participants on the 6 weeks dosing schedule will require a safety phone call at C1D22. The site is to record the call and any findings in the source documents. Further procedures / tests are to be scheduled by the site as clinically indicated and entered in an "unscheduled visit" module in the CRF. Refer to Section 8.3 for safety monitoring information for participants in closed arms.
Laboratory Assessments							
Hematology/Chemistry	X*	X	X	X			Collect predose. *Collect within 72 hours before C1D1 study intervention dose.
Urinalysis	X	X*	X*	X			*As clinically indicated.
Serum or Urine Pregnancy test (WOCBP only)	X	X	X	X			WOCBP require a negative test prior to C1. If more than 24 hours for a urine test or 72 hours for a serum test have elapsed prior to the first dose of study intervention, another pregnancy test is required. See country-specific requirements in Appendix 7.

Study Period:	Intervention		EOT	Posttreatment			Notes
Visit Number/Title:	Cycle 1	Cycles 2 to 17 (2 to 9 for Q6W schedule)		Safety FU	Efficacy FU	Survival FU	
Cycle Day	1	1	DC	30 days after last dose			
Scheduling Window (days):	±3	±3		+7	Q9W ±7	Q12W ±14	
PT/INR and aPTT/PTT (baseline only)	X						Within 72 hours of the first dose. Additional testing to be conducted as clinically indicated.
Thyroid Function Tests (TSH, T3, T4), Cortisol, and ACTH**		X	X	X			Free T3 and Free T4 are acceptable if total T3 and total T4 are unavailable. Retrospective review of thyroid function, ACTH and cortisol testing results is allowed when the results are not available before dosing. **ACTH testing is to be done per investigator's discretion.
Serum Tumor Marker (CEA)	X	X	X		X		Dosing permitted prior to results of CEA being known.
Biomarkers							
CCI [redacted]							

ACTH= adrenocorticotropic hormone; AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; C=cycle; CEA=carcinoembryonic antigen; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DBP=diastolic blood pressure; DC=discontinuation; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FU=follow-up; HR=heart rate; INR=international normalized ratio; MRI=magnetic resonance imaging; PT=prothrombin time; PTT=partial thromboplastin time; Q6W=every 6 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; SpO2=oxygen saturation; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

2 INTRODUCTION

CRC is a serious, life-threatening condition. Globally, the incidence of CRC reported in 2018 was ~1.8M (~10% of all cancers), and the number of worldwide cancer-related deaths due to CRC was ~881,000, making it the second leading cause of cancer death worldwide [Bray, F., et al 2018]. In the US, CRC is the third most common diagnosed cancer [Siegel, R. L., et al 2020]. It is estimated that 147,950 individuals will be newly diagnosed with CRC and 53,200 CRC deaths will occur in 2020 [Siegel, R. L., et al 2020a]. The annual age-adjusted incidence rate is 38.2 per 100,000 persons and the mortality rate is 13.9 per 100,000 persons [Siegel, R. L., et al 2020a] [National Cancer Institute 2020]. The median age at diagnosis is 67 years [National Cancer Institute 2020]. Stage at diagnosis is the most important predictor of survival. The 5-year relative survival rate for CRC was approximately 64% with only 14% for distant disease (22% of CRC patients at diagnosis) [National Cancer Institute 2020].

Mismatch repair deficient or MSI-H CRC comprises approximately 15% of CRC, whereas pMMR/MSS CRC comprises the remainder [Smyrk, T. C., et al 2001] [Xiao, Y. and Freeman, G. J. 2015]. When assessed stage-by-stage, the presence of MSI-H is noted in ~20% of Stage I/II, ~12% of Stage III, and only ~4% of Stage IV patients [Stadler, Z. K. 2015]. While dMMR/MSI-H CRC has a prognostic advantage in earlier stage disease, this advantage is less pronounced upon disease recurrence. Studies have shown that dMMR/MSI-H status is a disadvantage in advanced disease, with one study reporting significantly worse PFS and OS in participants with dMMR/MSI-H CRC compared with pMMR tumors (PFS: 6.2 vs 7.6 months; hazard ratio 1.33, 95% CI, 1.12-1.57; p=0.001; OS: 13.6 vs 16.8; hazard ratio 1.35, 95% CI, 1.13-1.61; p=0.001) [Venderbosch, S., et al 2014]. Recently, KEYNOTE-177 and KEYNOTE-164 demonstrated that pembrolizumab monotherapy showed significant efficacy in 1L or 2L+ (Section 2.2.3); however, even with this improvement in outcomes, there remains a need for still more progress.

2.1 Study Rationale

The efficacy of pembrolizumab in the treatment of advanced solid malignancies is well established. In addition, robust clinical activity of monotherapy pembrolizumab in participants with dMMR/MSI-H solid tumors, including CRC, has been shown in the KEYNOTE-016, -164, -158, and -177 studies.

The Phase 2 KEYNOTE-164 study [Le, D. T., et al 2019] studied pembrolizumab in participants with MSI-H mCRC. Participants had either 2 or more prior lines of therapy (Cohort A) or one or more prior lines of therapy (Cohort B); these cohorts enrolled 61 and 63 participants, respectively. Median PFS was 2.3 months (95% CI: 2.1 to 8.1 months) in Cohort A and 4.1 months (95% CI: 2.1 to 18.9 months) in Cohort B. Response rate was 33% in Cohort A and 35% in Cohort B (Cohort A, 95% CI: 21% to 46%; Cohort B, 95% CI: 23% to 48%). The median DOR was not reached in either cohort (Cohort A: NR (6.2-58.5+) and Cohort B: NR (4.4-52.4+)). Overall survival was 31 months in Cohort A and 47 months in Cohort B. Grade 3, 4 AE were seen in 16% of participants in Cohort A, and 13% of participants in Cohort B, the most common being pancreatitis, fatigue, and increased ALT and lipase. This data may be indicative of the effectiveness of anti-PD1 therapy in participants with MSI-H CRC. Though there was overlap of lines of therapy between the

2 cohorts, 38% of participants in Cohort B were treated after only 1 line of therapy, suggesting the possibility that earlier treatment with pembrolizumab had a salutary benefit [Le, D. T., et al 2019] [Le, D. T., et al 2021].

Pembrolizumab was also tested in MSI-H non-CRC as part of the KEYNOTE-158 study [Marabelle, A., et al 2019]. This study included 351 participants with 27 different MSI-H tumor types, the most common of which were endometrial, gastric, small intestine, and ovarian. ORR was 31%, with median PFS of 3.5 months and median OS of 20.1 months. Grade 3 to 5 AE occurring in 12.0% of participants (including 3 Grade 5 events) [Marabelle, A., et al 2019] [Maio, M., et al 2021]. This study showed that MSI-H status tumors may respond to anti-PD-1 checkpoint inhibition regardless of tumor type, and pembrolizumab is now approved by the FDA to treat MSI-H tumors agnostic to site of origin.

In the Phase 3 KEYNOTE-177, previously untreated patients with Stage IV dMMR/MSI-H CRC were randomized to treatment with chemotherapy (FOLFOX or FOLFIRI +/- cetuximab or bevacizumab) or to treatment with pembrolizumab [Andre, T., et al 2020]. In total, 307 patients were randomized. The primary endpoints were PFS and OS. At the time of the data cutoff for interim analysis, PFS at 12 months was 55.3% (95% CI: 47.0 to 62.9) and 37.3% (95% CI: 29.0 to 45.5) pembrolizumab and chemotherapy, respectively. PFS at 36 months was 42% and 11% for pembrolizumab and chemotherapy, respectively. Median PFS was 16.5 months (95% CI: 5.4 to 38.1 months) for pembrolizumab and 8.2 months (95% CI: 6.1 to 10.2 months) for chemotherapy, with a hazard ratio of 0.59 (95% CI: 0.45 to 0.79; *p*-value=0.0002). Likewise, the response rate by BICR favored the pembrolizumab arm (45.1% versus 33.1% in the chemotherapy arm). The effective crossover rate was of 60% in the ITT. Median OS was not reached (95% CI: 49.2 to NR) for pembrolizumab and 36.7 months (95% CI: 27.6 to NR) for chemotherapy, with a hazard ratio of 0.74 (95% CI: 0.53 to 1.03; *p*-value=0.0359; did not meet threshold for significance). All reported anatomic and molecular subgroups favored pembrolizumab, except for the RAS mutant tumors, which was not statistically significant. Toxicity was greater in the chemotherapy arm than the pembrolizumab arm, with Grade 3+ events occurring in 66% and 22%, respectively [Andre, T., et al 2021]. Based on this study, FDA, EMA have approved pembrolizumab monotherapy for treatment of mCRC in the first line setting.

These studies suggest that pembrolizumab is active in dMMR/MSI-H CRC, both in the front-line setting as well as in patients whose disease has previously been treated with chemotherapy. However, even with the improvement in outcomes from pembrolizumab in MSI-H CRC, there remains a need for still more progress. In the KEYNOTE-177 study, approximately 40% of participants treated with pembrolizumab progressed within 4 months of starting therapy, suggesting the presence of an MSI-H subgroup that is refractory to anti-PD-1 monotherapy. Another unmet need is treatment options for patients who initially respond to pembrolizumab monotherapy, but whose disease subsequently progresses despite continued treatment.

One potential approach to improving PD-1 efficacy includes adding a second checkpoint inhibitor such as anti-CTLA-4, LAG-3, TIGIT, and ILT4, make use of the different effects on the immune system from these different pathways. The design of this study allows for testing of several investigational agents in combination with pembrolizumab in

chemotherapy refractory and previously untreated participants with metastatic dMMR/MSI-H CRC.

Rationale for the use of Quavonlimab

An in vivo laboratory study, Fiegle and others [Fiegle, E., et al 2019] examined the effects of murine antibodies directed against PD-1, CTLA-4, or both together in an orthotopic xenograft model of murine colon cancer. In one experiment, dual inhibition, as compared with the use of either antibody alone, achieved the smallest growth of the primary tumor. Likewise, dual inhibition was most effective at preventing liver metastases, which appeared in 43% of mice given control intervention, as compared with 17% in mice treated with an anti-CTLA-4, 33% in mice treated with anti-PD1, and 0% in mice treated with both antibodies. Combination therapy likewise increased CD8+ T-cell infiltration and favorably shifted the macrophage population more than either agent alone.

One hypothesis, therefore, is that the addition of anti-CTLA-4 therapy to anti-PD1 agents may improve disease control of a cancer as compared with PD-1 monotherapy alone. This approach was the subject of the Phase 3 CheckMate 67 study [Larkin, J., et al 2019], which randomized untreated melanoma patients to either ipilimumab (3 mg/kg Q3W x 4 doses), nivolumab (1 mg/kg Q2W), or both in blinded fashion. Five-year survival was 52% in the combination group, as compared with 44% in the nivolumab group and 26% in the ipilimumab group.

There is evidence for a similar strategy in CRC. In one early nonrandomized study, participants with dMMR/MSI-H CRC [Lenz, H. J., et al 2020] were treated with nivolumab (3 mg/kg Q2W) and with ipilimumab (1 mg/kg Q6W x 4 doses) in the front-line setting. The radiologic response rate by BICR was 62%- and 24-month PFS was 74%, potentially outperforming PD-1 monotherapy, though the nonrandomized setting precludes a definitive assessment.

Based on this early data and given the high unmet need in patients with dMMR/MSI-H CRC, the present study has been designed to examine the efficacy of MK-1308A in participants with dMMR/MSI-H Stage IV mCRC whose tumors are chemotherapy refractory (Cohort A) or previously untreated (Cohort B). For additional information, refer to the MK-1308 IB.

Rationale for the use of Favezelimab

LAG-3 may also be an appropriate target for combination treatment with anti-PD-1 agents. In a mouse model, LAG-3 appears to play an immunosuppressive role, helping to prevent autoimmunity [Topalian, S. L., et al 2012]. CD8+ T-cells expressing both LAG-3 and PD-1 are the dominant TIL population in mice transplanted with CT26 colon carcinoma cells, in which LAG-3 was shown to control T-cell proliferation/cell cycle progression, resulting in a state of hypofunction of these immune cells [Waugh, K. A., et al 2016]. Consistent with the landmark finding that immune cells within human colorectal tumors predict clinical outcome [Galon, J., et al 2006], both in vitro and in vivo data indicate that dual blockade of LAG-3 and PD-1 potentially can have a synergistic impact on reversing tumor-specific anergy [Andrews, L. P., et al 2017]. In one example, using the MC-38 mouse model of colon derived

tumor cells, PD-1 inhibition resulted in expression of LAG-3 on T-cells [Beyrend, G., et al 2019]. In turn, combined PD-1 and LAG-3 blockade delayed tumor growth and enhanced survival.

Clinical evidence for LAG-3/PD-1 dual blockade appears to match this preclinical data. The RELATIVITY-047 study [Lipson, E. J., et al 2021] treated 1L advanced melanoma participants with either nivolumab (control arm) or nivolumab + relatlimab (experimental arm). The study met its primary endpoint demonstrating superior PFS by BICR with nivolumab + relatlimab (median PFS = 10.1 months) compared with nivolumab alone (median PFS = 4.6 months), HR (95% CI) = 0.75 [0.6 – 0.9]; p=0.0055). The combination showed a manageable safety profile without unexpected safety signals.

LAG-3 in Colorectal Cancer

In CRC patients, LAG-3 was overexpressed on colorectal immune cells, and correlated with poor differentiation, advanced stage, lymph node involvement, and depth of invasion (T stage) [Chen, J. and Chen, Z. 2014]. LAG-3 expression was notably greater in MSI-H than MSS CRC tumors [Llosa, N. J., et al 2015] and was associated with shorter relapse-free survival and tumor cell PD-L1 expression [Lee, S. J., et al 2017].

The MK-4280-001 study evaluated the combination of LAG-3 inhibition with PD-1 inhibition in colorectal cancer. This is a Phase 1 nonrandomized, multi-site, open-label study of favezelimab (MK-4280) as monotherapy, in combination with pembrolizumab by sequential administration or in coformulation with pembrolizumab (MK-4280A), with or without chemotherapy or lenvatinib. Part A was a dose escalation study in participants with advanced solid tumors for whom no standard of care is available; Part B was conducted in participants with select solid tumors. Included in Part B were 2 cohorts of patients with metastatic colorectal cancer who were treated either with favezelimab monotherapy (800 mg) or in combination/coformulation with 200 mg pembrolizumab. Eligible participants had MSS PD-1/PD-L1-treatment-naïve mCRC that progressed on all prior therapies (3L+). Treatment continued for 35 cycles or until progression, unacceptable toxicity, or investigator/participant decision to withdraw from study intervention. Crossover from favezelimab monotherapy to pembrolizumab + favezelimab doublet therapy was permitted.

Patient outcomes were presented at the 2021 ASCO meeting [Garralda, E., et al 2021]. A total of 100 patients were enrolled, 20 of whom received favezelimab monotherapy while the remainder received either combination or coformulation treatment. Nine monotherapy patients crossed over from monotherapy to combination therapy.

At data cutoff, median follow-up was 5.8 months in the favezelimab arm and 6.2 months in the favezelimab + pembrolizumab/MK-4280A arms. TRAEs were 65.0% with favezelimab and 65.2% with favezelimab + pembrolizumab/MK-4280A. Grade ≥3 TRAEs were 15.0% (favezelimab), and 20% favezelimab + pembrolizumab/MK-4280A). No Grade 5 TRAEs were reported. Common TRAEs (≥15.0%) included fatigue (20.0%) and nausea (15.0%) with favezelimab, and fatigue (16.9%) with favezelimab + pembrolizumab/MK-4280A.

The efficacy population included 20 participants who received favezelimab monotherapy and 80 participants who received favezelimab + pembrolizumab, of which 12 and 36 participants, respectively, had PD-L1 CPS ≥1 tumors. Confirmed ORR was 0% in participants receiving favezelimab and 6.3% (4 PR, 1 CR) with favezelimab + pembrolizumab/MK-4280A. The ORR was 11.1% (4 of 36) among the doublet therapy participants whose tumors expressed PD-L1 CPS≥1. Only one response was seen among the 35 patients with PD-L1 CPS score <1. In the favezelimab + pembrolizumab/MK-4280A arms, median DOR was 10.6 months (range: 5.6-12.7 months). The median OS and 12 months OS rate in participants who received favezelimab + pembrolizumab/MK-4280A was 8.3 months (range: 5.5-12.9 months) and 40.8% in the ITT population, and 12.7 months (range: 4.5 months-NR) and 50.6% in participants with tumors expressing PDL-1 CPS≥1. The median PFS and 6-month PFS rate in participants receiving favezelimab +pembrolizumab/MK-4280A was 2.1 months (range: 1.9-2.2 months) and 16.2% in the ITT population, and 2.2 months (range: 1.8-4.2 months) and 25.4% in participants with tumors expressing PD-L1 CPS≥1 [Garralda, E., et al 2021].

Overall, favezelimab alone or in combination with pembrolizumab had a manageable safety profile, with no treatment-related deaths. Promising antitumor activity was observed with favezelimab + pembrolizumab/MK-4280A therapy compared with monotherapy and was enhanced in participants with PD-L1 CPS ≥1 tumors [Garralda, E., et al 2021].The above data provide the rationale for a combination therapy targeting the PD-1 and LAG-3 pathways in previously untreated participants with metastatic dMMR/MSI-H CRC, particularly among those with PD-L1 positive tumors. For additional information, refer to the MK-4280 IB.

Rationale for the use of TIGIT

Enhancing the proven anti-PD-1 immune stimulatory mechanism through a novel mechanism of action is therefore an attractive scientific concept. One avenue for further investigation is the T-cell stimulatory/inhibitory network TIGIT (PVRIG/TACTILE)-CD226 (DNAM1) pathway. Antibody blockade of TIGIT, a T-cell inhibitory receptor within this network, has shown promising activity in preclinical cancer models, as well as in clinical studies.

Vibostolimab (MK-7684) is a humanized IgG1 that blocks the inhibitory checkpoint receptor TIGIT expressed on T-cells and NK cells. Preclinical data has demonstrated that anti-TIGIT mTIGIT antibodies on the mIgG2a backbone (with high affinity FcγR binding) are more efficacious than anti-TIGIT mTIGIT antibodies on the IgG1 D265A backbone (without FcγR binding) as single agents and in combination with mDX400 (anti-PDmPD-1 antibody) in multiple preclinical tumor models. Therefore, a strong rationale exists to develop anti-PD-1 and anti-TIGIT combination therapies.

MK-7684 is being developed in MK-7684-001, which is a safety, efficacy, and PK study examining MK-7684 as monotherapy and in combination with pembrolizumab or with pembrolizumab plus chemotherapy in adults with metastatic solid tumors for which there are no available therapies expected to convey clinical benefit. This study consists of a Part A dose escalation phase and a Part B expansion phase which intends to assess the antitumor efficacy of MK-7684 at the RP2D of 200 mg when used as monotherapy and in combination with pembrolizumab in distinct tumor indications, including CRC.

Clinical activity was observed at the 200-mg and 700-mg dose levels of vibostolimab in participants with advanced solid tumors, particularly, in PD-1/PD-L1 inhibitor treatment-naïve participants with NSCLC and cervical cancer treated with vibostolimab in combination with pembrolizumab. In preliminary efficacy analyses based on PD-L1 status, treatment with vibostolimab in combination with pembrolizumab had promising ORR in PD-1/PD-L1 inhibitor treatment-naïve participants with PD-L1 positive (TPS≥1%) NSCLC (30.8%) and PD-L1 positive (TPS≥1% or MIDS≥2%, equivalent to CPS≥1%) cervical cancer (20.8%).

As of 15-APR-2021, available safety data show that vibostolimab has generally been tolerable. The incidence and types of AE observed after treatment with vibostolimab in combination with pembrolizumab and SOC chemotherapy were generally consistent with those expected after treatment with pembrolizumab plus SOC chemotherapy (for additional information, refer to the MK-3475 IB). The safety profile of participants treated with MK-7684A was consistent with the known safety profile of participants treated with 200 mg vibostolimab in combination with 200 mg pembrolizumab administered sequentially.

TIGIT in Colorectal Cancer:

Preclinical evidence for the combination in CRC is provided by Liang and others, who showed that TIGIT was upregulated in colorectal cancer infiltrating lymphocytes, including CD3, CD4, CD8, and NK cells [Liang, R., et al 2021]. Moreover, CD4+ TILs from patients with MSI-H tumors showed significantly higher expression of TIGIT (MSI-H; 47.3 +/- 3.3 vs MSS; 34.8 +/- 1.9) than MSS CRC cells [Toor, S. M., et al 2021].

Clinical efficacy in CRC was seen in the MK-7684-001 study. As of 15-APR-2021, preliminary efficacy data were available for a total of 42 PD-1/PD-L1 treatment-naïve participants. These individuals were given 200 mg of vibostolimab in combination with 200 mg pembrolizumab. The best overall response included 2 confirmed responses (4.8%) with 1 CR and 1 PR; both of these participants had MSI-H tumors. An additional 11 participants experienced stable disease.

The Sponsor hypothesizes, therefore, that dual blockade with vibostolimab and pembrolizumab will offer substantially augmented antitumor efficacy in previously untreated participants with metastatic dMMR/MSI-H CRC. Additional details regarding benefits and risks for participants seen in other ongoing studies of MK-7684 can be found in the IB.

Rationale for the use of ILT4

MK-4830 is a novel fully human IgG4 mAb that is an antagonist of ILT4, for the treatment of solid tumors.

In CRC, ILT4 is overexpressed in 68% of human CRC tumor samples and the coexpression of ILT4 and HLA-G are correlated with higher TNM stage (66% Stage III/IV) as compared with ILT4- patients (43% Stage III/IV) [Cai, Z., et al 2019]. ILT-4 expression is associated with shorter overall survival among both Stage I-II CRC patients as well as Stage III-IV CRC patients [Chen, Q. Y., et al 2021].

Antagonism of ILT4 has shown to enhance proinflammatory response and to inhibit myeloid dependent suppression on effector T-cells [Chen, H. M., et al 2018]. Anti-ILT4 and anti-PD-1 combination significantly decreased the granulocytic MDSC population and Treg populations in tumor tissue, inhibiting tumor progression and modulating the tumor microenvironment, substantially decreasing tumor burden in different xenograft lung cancer models. Therefore, relief of myeloid immune suppression may improve antitumor efficacy, potentiate T-cell activation and improve the efficacy of T-cell-targeted therapies such as pembrolizumab, even in tumors that do not normally respond to PD-1 antagonism alone.

In a Phase 1 dose-escalating study, 50 participants with advanced solid tumors received MK-4830 as monotherapy and 34 participants received MK-4830 in combination with pembrolizumab. Preliminary data show that of the 50 participants treated with MK-4830 monotherapy in the initial treatment phase, the BOR (with response confirmation) was a PR for 1 participant. (2.0%). The time to response for this participant was 17.6 weeks and the duration of response was greater than 24 weeks. In addition, 11 participants (22.0%) treated with MK-4830 monotherapy experienced SD. Preliminary data also show that of the 34 participants treated with MK-4830 and pembrolizumab combination therapy in the initial treatment phase, the BOR (with response confirmation) was CR for 1 participant (2.9%) and PR for 7 participants (20.6%). In addition, 9 participants (26.5%) treated with MK-4830 and pembrolizumab combination therapy experienced SD.

Additionally, 18 participants initially treated with MK-4830 monotherapy crossed over to receive MK-4830 and pembrolizumab combination therapy. Of these, 4 participants had an evaluable efficacy assessment at the time of the data cutoff; the best overall response for 1 participant was PR. One participant experienced SD and 2 participants experienced PD.

Overall, for the 9 participants treated with MK-4830 and pembrolizumab combination therapy that had a response (CR or PR) in either the initial treatment phase or in crossover, the median time to response was 17.1 weeks (range: 5.3-21.7 weeks). The median duration of response was 68.9 weeks, and ranged from 27.1 to greater than 85.9 weeks, ie, all 9 participants had an extended response duration of greater than ≥24 weeks.

Of the 276 participants treated in the study as of the 15-MAR-2021 data cutoff date, 142 participants (51.4%) had 1 or more drug-related AEs. The most common study-drug-related AEs in all participants were fatigue, diarrhea, hypothyroidism, pruritus, rash, and nausea. Grade 3 drug-related AEs that occurred in more than 1 participant included aspartate aminotransferase increased (in 4 participants), fatigue and aspartate aminotransferase increased (in 3 participants each) and fatigue, diarrhea, pneumonia, and alanine aminotransferase increased (in 2 participants each). There was 1 Grade 4 AE (respiratory failure) and 2 Grade 5 AEs (pneumonia) that were considered by the investigator to be drug-related. Eight participants experienced 9 drug-related SAEs (pneumonia, respiratory failure, diarrhea, pneumonitis, colitis, and enterocolitis). Five participants discontinued treatment due to a drug-related AE(s). One or more AEOSI was reported for 4 participants in the MK-4830 monotherapy group, 37 participants in the MK-4830 and pembrolizumab combination therapy group.

This evidence suggests that removal of immune suppression induced by MK-4830 combined with the T-cell checkpoint inhibitor, pembrolizumab, could offer substantially augmented antitumor efficacy in patients with dMMR/MSI-H CRC. For additional information, refer to the MK-4830 IB.

This protocol is specific for patients with metastatic disease. While patients with nonmetastatic but locally advanced disease might benefit from these treatments, the heterogeneity anticipated by inclusion of the unresectable group would skew the results of the arms in this small study.

2.2 Background

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with its ligands PD-L1 and PD-L2. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions.

Clinical safety, tolerability, and support for the selected dosing regimen may be found with other detailed background information in the IB/approved labeling.

2.2.1.2 Quavonlimab

Quavonlimab is a humanized IgG1/kappa monoclonal antibody that binds to CTLA-4, blocking the interaction of CTLA-4 with either of its ligands, CD80 (B7.1) and CD86 (B7.2). CTLA-4 is a negative regulator of T-cell function and proliferation and is found on the surface of activated T-cells and Tregs.

CTLA-4 suppression is thought to be primarily at sites of T-cell activation, eg, secondary lymph organs rather than within the tumor microenvironment. However, inhibition of CTLA-4 results in substantial increases of T-cell infiltrates within tumor tissues. This contrasts with the presumed inhibition of T-cell function via PD-1 engagement, which occurs within the tumor microenvironment between T-cells interacting with both APC and the tumor cells themselves. Furthermore, CTLA-4 inhibitors can engage ex vivo FcγRIIIA (CD16)-expressing, nonclassical monocytes resulting in ADCC-mediated lysis of Treg cells. Treg cells are essential in maintaining self-tolerance; however, they can also promote tumor progression by suppressing antitumor immunity. The Treg cell-depleting function of CTLA-4 inhibitors may also contribute to the clinical benefit of those agents [Togashi, Y., et al 2019].

Clinical safety, tolerability, and support for the selected dosing regimen may be found with other detailed background information in the IB.

The Sponsor has developed a coformulated product of quavonlimab and pembrolizumab (referred to as MK-1308A). MK-1308A is a fixed-dose combination of quavonlimab and pembrolizumab antibodies being evaluated in 1 ongoing clinical study, MK-1308-001 (Arms I, J, and K) and also additional studies now beginning in various tumor types.

2.2.1.3 Favezelimab

MK-4280 (favezelimab) is an IgG4/kappa monoclonal antibody that binds to the immune checkpoint receptor LAG-3 and blocks the interaction of LAG-3 with MHC Class II ligands. LAG 3 itself is an inhibitory immune modulatory receptor that regulates effector T-cell homeostasis, proliferation, and activation, and has a role in the suppressor activity of Tregs. LAG-3 is expressed on activated CD8+ and CD4+ T-cells, Tregs and the Tr1 regulatory T-cell population, as well as on natural killer cells and a subset of tolerogenic plasmacytoid dendritic cells. Because of its proposed role on both effector T-cells and Tregs, LAG-3 is one of several immune checkpoint molecules where simultaneous blockade of both cell populations has the potential to enhance antitumor immunity.

Clinical safety, tolerability, and support for the selected dosing regimen may be found with other detailed background information in the IB.

Given the Sponsor's observation of enhanced antitumor activity of anti-LAG-3 when combined with PD-1 blockade in nonclinical models, the Sponsor has developed a coformulated product of favezelimab and pembrolizumab (referred to as MK-4280A). MK-4280A is a fixed-dose combination of favezelimab and pembrolizumab antibodies. The single vial presentation could provide significant benefit to patients and providers, including simplified preparation and reduced infusion times compared with separate formulations.

2.2.1.4 Vibostolimab

Vibostolimab is a humanized, antagonistic IgG1 mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligand, CD155/PVR. TIGIT is one of multiple immune checkpoint molecules that maintain immune homeostasis and prevent uncontrolled immune activation.

MK-7684 binds to human and cynomolgus monkey TIGIT and was selected based on its binding affinity and ability to inhibit TIGIT-mediated activity.

TIGIT and CD226/CD96 form a comodulatory network in which TIGIT provides inhibitory signaling and CD226/CD96 provides stimulatory signaling. TIGIT is expressed on CD8+, CD4+, and Treg T-cell subpopulations. Because of its inhibitory role on T-cells, blockade of this receptor has the potential to enhance tumor killing.

Clinical safety, tolerability, and support for the selected dosing regimen may be found with other detailed background information in the IB.

Given the observed efficacy and tolerability of vibostolimab when used in combination with pembrolizumab in Study MK-7684-001, the Sponsor developed MK-7684A, a fixed-dose coformulated product of 200 mg vibostolimab and 200 mg pembrolizumab supplied in a

single-use drug product vial. Based on available safety data and the results of preliminary PK analysis, the Sponsor considers MK-7684A to be sufficiently comparable to sequentially administered vibostolimab and pembrolizumab. Compared with sequential administration of separate formulations, the single coformulation vial could provide significant benefit to patients and providers, including simplified preparation, reduced infusion times, and reduction of potential errors in drug administration.

2.2.1.5 MK-4830

MK-4830 is a novel, first-in-class, fully human IgG4 mAb with high specificity of binding to the ILT4 receptor, thus inhibiting its interactions with MHC class I molecules including HLA-G. The interaction of ILT4 with HLA-G promotes signaling through immunoreceptor tyrosine-based inhibitory motifs via activation of SHP-1. This signaling can antagonize immunoreceptor tyrosine-based activation motif receptor-mediated activation of myeloid cells [Colonna, M,, et al 1998]. ILT4 signaling may directly inhibit the function of monocytes, dendritic cells and neutrophils, thus impairing the innate immune antitumor response.

Clinical safety, tolerability, and support for the selected dosing regimen may be found with other detailed background information in the IB.

2.2.1.6 Rationale for Coformulations

MK-1308A, MK-4280A, and MK-7684A are coformulations of the respective drugs and pembrolizumab in a single vial. The rationale to develop these single entity products as an FDC includes the following points:

CCI

For more details refer to the MK-1308A, MK-4280A, and MK-7684A IB.

2.2.2 Preclinical and Clinical Studies

Refer to the respective IBs for preclinical and clinical study data for quavonlimab, pembrolizumab, favezelimab, vibostolimab, and MK-4830.

2.2.3 Ongoing Clinical Studies

Refer to the respective IBs for ongoing clinical study data for quavonlimab, pembrolizumab, favezelimab, vibostolimab, and MK-4830.

2.3 Benefit/Risk Assessment

Pembrolizumab monotherapy has shown significant activity in the setting of dMMR/MSI-H mCRC in both first line and later settings. However, the benefit is not universal; in the KEYNOTE-177 study approximately 40% of participants showed disease progression soon after beginning treatment.

The addition of a CTLA-4 antibody (ie, ipilimumab), in an uncontrolled dMMR/MSI-H cohort, has appeared to increase the effectiveness of immunotherapeutic approaches against these tumors. Participants with dMMR/MSI-H CRC treated with both CTLA-4 and PD-1 inhibition had a response rate of 62% and 12-month PFS of 76% [Lenz, H. J., et al 2020] whereas pembrolizumab monotherapy had a response rate of 44% and 12-month PFS of 55% [Andre, T., et al 2020]. However, these approaches have never been directly compared, which is the goal of this study.

The existing preclinical and early clinical data suggest that inhibiting other immune checkpoint molecules in combination with PD-1 blockade is a promising therapeutic strategy and that the risk/benefit assessment for participants in this study will be favorable.

Phase 1 studies have shown that MK-4830 and MK-7684 as monotherapy or in combination with pembrolizumab can potentially enhance antitumor efficacy in patients with solid tumors (refer to respective IBs and Section 2.1). Also, preliminary results support the use of MK-1308 and MK-4280 in combination with pembrolizumab (refer to respective IBs and Section 2.1). An advantage of the platform study design is that it will allow rapid, concurrent evaluation of multiple investigational agents in chemotherapy refractory and previously untreated participants with metastatic dMMR/MSI-H CRC. This may identify new combination interventions with improved responses over those historically achieved with current treatment options. Therefore, a potential benefit may be faster clinical development of novel interventions benefiting this particular patient population, while reducing exposure of participants to interventions that do not show improved clinical benefit. Nevertheless, combination therapy might prove to have greater toxicity rates, particularly with respect to colitis and hepatitis. A goal of this study will be to formally assess AE and SAE rates.

It cannot be guaranteed that participants in clinical studies will directly benefit from this treatment, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. Potential risks of these novel combination interventions may be increased toxicity, intolerability, or unanticipated adverse drug reactions. Each agent has been evaluated in combination with pembrolizumab to support the doses planned for this study and no new safety signals have been identified with these combinations compared with pembrolizumab monotherapy (Section 2.1). Considering the high unmet need for new and tolerable treatment options, the benefit-risk assessment for participants in this study is considered to be favorable.

As per the Investigator Letter dated 25-SEP-2023, the MK-4830+pembrolizumab arm was closed to enrollment; all ongoing participants were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy. This decision was based on a lack of clinical efficacy of MK-4830 in combination with pembrolizumab in several tumor types across all MK-4830-related studies and not on any concerns about the safety of this combination.

More recently and as briefly described in the Investigator Letter dated 16-DEC-2024, 4 Phase 3 studies met prespecified futility criteria for OS or RFS: Study MK-7684A-003 in metastatic NSCLC with PD-L1 TPS ≥50% (OS HR=1.06; 95% CI: 0.83, 1.35), Study MK-7684A-007 in metastatic NSCLC with PD-L1 TPS ≥1% (OS HR=1.14; 95% CI: 0.87, 1.50), Study MK-7684A-008 in ES-SCLC (OS HR=1.26; 95% CI: 1.00, 1.59; presented at Society for Immunotherapy of Cancer 2024), and Study MK-7684A-010 in adjuvant melanoma (RFS HR=1.25; 95% CI: 0.87, 1.80; presented at Society for Melanoma Research 2024) (data on file). Overall, the lack of efficacy observed with MK-7684A rendered the risk-benefit balance unfavorable, so treatment with this investigational therapy is being stopped in all studies. This decision is not based on any concerns about the safety of MK-7684/MK-7684A.

In addition and as briefly described in the Investigator Letter dated 16-DEC-2024, after careful consideration, the Sponsor decided to end the MK-4280A clinical development program. This decision was made after a thorough evaluation of data from the favezelimab clinical program and is not based on any concerns about the safety of this fixed-dose combination.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying investigational agents and pembrolizumab IBs and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male and female participants who are at least 18 years of age, with mismatch repair deficient or microsatellite instability-high Stage IV colorectal cancer who have measurable disease per RECIST 1.1 by Blinded Independent Central Review, and who are either chemotherapy refractory (Cohort A), or have received no prior lines of systemic therapy for Stage IV disease (Cohort B).

Primary Objectives	**Primary Endpoints**
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Objective Response Rate per RECIST 1.1 as assessed by Blinded Independent Central Review	Objective Response: Complete Response or Partial Response
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Objective Response Rate per RECIST 1.1 as assessed by Blinded Independent Central Review	Objective Response: Complete Response or Partial Response
Secondary Objectives	**Secondary Endpoints**
Objective (Cohorts A and B): To evaluate Duration of Response per RECIST 1.1 as assessed by Blinded Independent Central Review	The time from first documented evidence of Complete Response or Partial Response until disease progression or death due to any cause, whichever occurs first
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Progression-Free Survival per RECIST 1.1 as assessed by Blinded Independent Central Review	Progression-Free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Progression-Free Survival per RECIST 1.1 as assessed by Blinded Independent Central Review	Progression-Free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Progression-Free Survival per RECIST 1.1 as assessed by the investigator	Progression-Free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Progression-Free Survival per RECIST 1.1 as assessed by the investigator	Progression-Free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Objective Response Rate per RECIST 1.1 as assessed by the investigator	Objective Response: Complete Response or Partial Response
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Objective Response Rate per RECIST 1.1 as assessed by the investigator	Objective Response: Complete Response or Partial Response
Objective (Cohort A and B): To evaluate Duration of Response per RECIST 1.1 as assessed by the investigator	The time from first documented evidence of Complete Response or Partial Response until disease progression or death due to any cause, whichever occurs first
Objective (Cohort A): To compare MK-1308A and pembrolizumab monotherapy with respect to Overall Survival	Overall Survival: The time from randomization to death due to any cause
Objective (Cohort B): To compare MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and pembrolizumab monotherapy with respect to Overall Survival	Overall Survival: The time from randomization to death due to any cause
Objective (Cohort A): To evaluate the safety and tolerability of MK-1308A compared to pembrolizumab monotherapy	Adverse Events Study intervention discontinuation due to Adverse Events

Objective (Cohort B): To evaluate the safety and tolerability of MK-1308A, MK-4280A, MK-7684A, MK-4830+Pembrolizumab, and compared to pembrolizumab monotherapy	Adverse Events Study intervention discontinuation due to Adverse Events
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

CCI

[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, randomized, active-controlled, parallel-group, multisite, open-label study of MK-1308A and pembrolizumab monotherapy (Cohort A) or various investigational agents and pembrolizumab monotherapy (Cohort B) in participants who are at least 18 years of age with dMMR/MSI-H Stage IV CRC, who have measurable disease per RECIST 1.1 as assessed by the site and verified by BICR, and who are either chemotherapy refractory (Cohort A) or have received no prior lines of systemic therapy for Stage IV disease (Cohort B).

Colorectal tumor MMR/MSI status will be tested locally as clinically indicated as per NCCN, ESMO, and ASCO guidelines [National Comprehensive Cancer Network 2019] [National Comprehensive Cancer Network 2019a] [Balmana, J., et al 2010] [Stoffel, E. M., et al 2015]. Randomization of participants will be stratified based on tumor RAS status (mutant versus WT).

Overall, approximately 320 participants will be enrolled in the study:

- Cohort A, CCI participants will be randomized 1:1 to either MK-1308A or pembrolizumab monotherapy
- Cohort B, CCI participants will be randomized 1:1:1:1:1 to the following investigational agents:
  - Pembrolizumab monotherapy
  - MK-1308A
  - MK-4280A
  - MK-7684A
  - MK-4830+pembrolizumab (as of 22-SEP-2023, this arm was closed to enrollment with CCI participants randomized)

MK-1308A or pembrolizumab monotherapy will be administered Q6W for approximately 2 years or until a discontinuation criterion is met. MK-4280A, MK-7684A, and MK-4830+pembrolizumab will be administered Q3W for approximately 2 years or until a discontinuation criterion is met.

No treatment crossover is planned for the study.

Participants who require interruption of MK-1308A, MK-4280A, MK-7684A, or MK-4830+pembrolizumab treatment for toxicity, who then recover, may either resume their assigned treatment or may initiate pembrolizumab monotherapy at the discretion of the investigator and with Sponsor consultation.

Depending on the totality of accumulated and emerging data from this and other studies, the Sponsor may close enrollment to one or more study arms prior to full enrollment. While the

Sponsor may elect to close an arm, the enrollment or study procedures for other arms of the study will remain unaffected. In addition, there are no current plans to add more cohorts or to expand the existing cohorts in this study. At implementation of Amendment 05, the following treatment arms are considered closed: Cohort B: MK-4280A, Cohort B: MK-7684A, and Cohort B: MK-4830+pembrolizumab.

As of the Investigator Letter dated 16-DEC-2024, participants who were receiving MK-4280A were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy, and participants who were receiving MK-7684A were discontinued from that study therapy and offered the option to transition to pembrolizumab monotherapy. As per the Investigator Letter dated 25-SEP-2023, the MK-4830+pembrolizumab arm was closed to enrollment; all ongoing participants were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy.

Participants who opt to continue treatment with pembrolizumab monotherapy will remain on the same visit schedule as per the initial assignment.

Participants in closed arms with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Participants in closed arms who are benefiting from pembrolizumab monotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab monotherapy until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.

Participants will be evaluated with tumor scans and RECIST 1.1 response assessment (chest, abdomen, and pelvis) Q9W (63 ±7 days) from the date of allocation until disease progression is assessed by the site and verified by BICR or initiation of a new anticancer treatment. All scans obtained will be assessed by the BICR using RECIST 1.1 for determination of ORR and PFS. Refer to Section 8.2.1 for imaging information for participants in closed arms.

Survival follow-up will continue after disease progression is verified by BICR or the start of new anticancer treatment for participants in open arms. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study. Refer to Section 8.11.4 for posttreatment follow-up information for participants in closed arms.

Discontinuation of study treatment may be considered for participants who achieve CR per RECIST 1.1 by 2 tumor scans at least 4 weeks apart, were treated with at least 4 cycles (if dosed Q6W) or 8 cycles (if dosed Q3W) of study intervention before discontinuing treatment and received at least 1 treatment (Q6W) or 2 treatments (Q3W) beyond the date when the initial CR was declared.

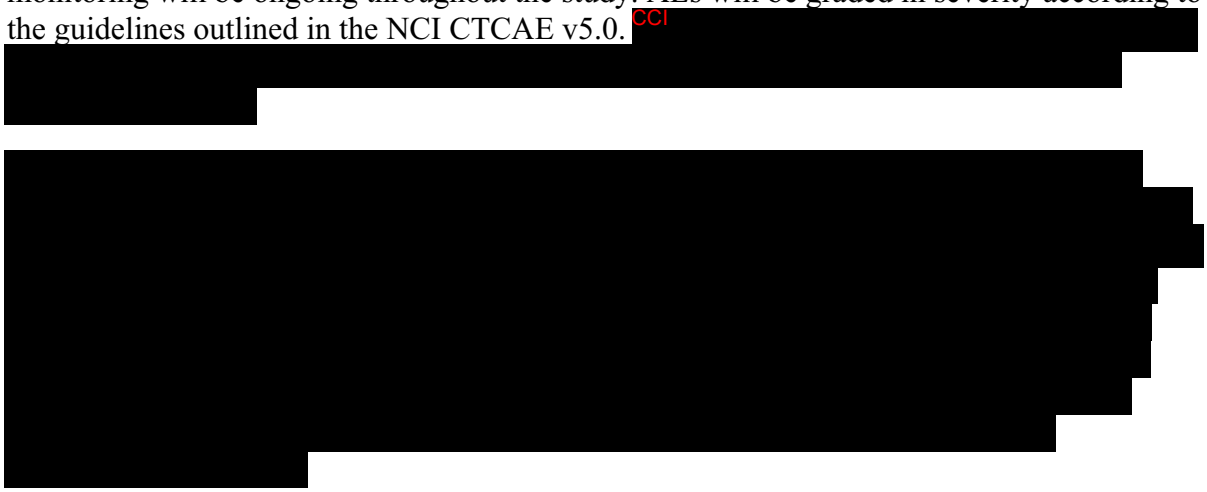
Participants who stop study intervention after a CR and who later progress, and participants who show PR or SD throughout the first 2 years of treatment and who progress after completing therapy may be eligible for the Second Course Phase. Refer to Section 6.1.1.2 for additional details and for Second Course treatment information for participants in closed arms.

Participants may undergo resection of the primary tumor and/or metastasectomy with curative intent after achieving a response to study intervention that converts previously unresectable disease to resectable disease, if deemed eligible per investigator's discretion in a multidisciplinary approach according to his/her institutional standard, and with Sponsor consultation. After surgery, when clinically appropriate and after the surgical wound is fully healed, the participant may resume the same therapy they were receiving pre-operatively starting at least 4 weeks and no more than 12 weeks post-surgery, unless approved by the Sponsor.

Post-operative therapy may continue until verified progression by BICR, intolerability, or completion of the assigned number of cycles of treatment (as per study arm).

The first post-operative tumor scan should be performed at a minimum of 4 weeks after surgery and no more than 8 weeks after surgery and before the start of the next treatment cycle (Section 8.2.1.2). If treatment does not resume within 12 weeks after surgery, the investigator should consult with the Sponsor. In addition, participants who discontinue study intervention for reasons other than radiographic disease progression will have posttreatment follow-up for disease status Q9W (± 7 days) from date of randomization until disease progression (verified in an expedited manner by BICR, for participants in open arms, per RECIST 1.1), start of a non-study anticancer therapy, consent withdrawal, becoming lost to follow-up, death, or end of the study, whichever occurs first.

The primary endpoint of the study will be ORR per RECIST 1.1 as assessed by BICR. Secondary endpoints will include DOR and PFS as assessed by BICR, OS, ORR as assessed by investigator, PFS as assessed by investigator, and safety and tolerability of the study interventions. Safety evaluations will include AE monitoring, physical examinations, clinical laboratory parameters, vital signs, and assessment of ECOG Performance Status. AE monitoring will be ongoing throughout the study. AEs will be graded in severity according to the guidelines outlined in the NCI CTCAE v5.0. CCI



This study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Response rate has been a traditional endpoint for studies of oncologic drugs. The availability of clinical response rates from preceding studies will allow an indirect comparison of data acquired in this study with that seen in the earlier studies noted above. This study will use ORR based on RECIST 1.1 criteria as assessed by BICR as the primary endpoint. ORR is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess ORR is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments.

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

Secondary efficacy endpoints for this study include DOR and PFS, based on RECIST 1.1 as assessed by BICR, and OS.

PFS is likewise a validated endpoint for cancer studies generally and may be particularly appropriate for checkpoint inhibitor studies. Ritchie et al. (2018) showed that PFS may indeed correlate more closely with OS than response rate [Ritchie, G., et al 2018]. As with OR, the PFS seen among these patients will be considered with the historical data available.

Of note, LS patients have an underlying predilection to forming additional malignancies including stomach, liver, brain, and endometrial cancers, among others. A new lesion that appears in a LS patient that the investigators suspect to be a de novo LS related second malignancy rather than progression of CRC metastases should be investigated by the treating physicians and the Sponsor should be notified of the event. However, as an exception to the discontinuation provisions outlined in Section 7.1, participants do not necessarily need to end study treatment in this circumstance. If the second malignancy can be appropriately addressed per NCCN, ASCO, or ESMO guidelines to the point where no further therapy is required (eg, after a hysterectomy + brachytherapy for a Stage I endometrial cancer), and if the participant continues to otherwise meet inclusion/exclusion criteria (except the second malignancy exclusion criteria), the participant may then be eligible to resume protocol treatment until the discontinuation provisions in Section 7.1 are again met. Resumption of treatment must be performed in consultation with the Sponsor. During workup and treatment of a possible second LS malignancy, scheduled scans should be continued as an exception to the imaging provisions set forth in Section 8.2.1.3.

4.2.1.2 Safety Endpoints

Safety is a secondary endpoint of the study.

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

4.2.1.3 Patient-reported Outcomes

CCI [redacted]

4.2.1.3.1 EuroQoL EQ-5D-5L

CCI [redacted]

4.2.1.3.2 EORTC QLQ-C30

CCI [redacted]

4.2.1.4 Pharmacokinetic Endpoints

CCI [redacted]

4.2.1.5 Planned Exploratory Biomarker Research

CCI [redacted]

CCI [redacted]

4.2.1.6 Future Biomedical Research

CCI [redacted]

CCI [redacted]

4.2.2 Rationale for the Use of Comparator

Cohort A will compare response rates in participants treated with PD-1 monotherapy (pembrolizumab) with those treated with the PD-1/CTLA-4 doublet. As no prior studies have directly compared these 2 strategies in dMMR/MSI-H CRC, this study will provide the first set of randomized data toward assessing the efficacy of these 2 approaches. Pembrolizumab may be considered the current standard of care in this setting based on KEYNOTE-164, which showed efficacy of pembrolizumab in 2L and 3L settings. Cohort B will compare response rates in participants treated with pembrolizumab monotherapy with those treated with the other investigational agents. Pembrolizumab may be considered as the current standard of care in this population based on KEYNOTE-177 results.

4.2.3 Rationale for RAS Stratification

CCI [redacted]

4.2.4 Rationale for Open-label Study

Participants will not be blinded as to their treatment assignments. The rationale for this is that (1) all participants will receive at least anti-PD-1 therapy, which has received regulatory approval for this indication in many countries, and therefore it is anticipated that few participants will opt to leave the study based on their treatment assignment; (2) an open-label design affords investigators the option to change from combination treatment to PD-1 monotherapy in response to toxicity; and (3) there will be logistical difficulties / additional participant burden with blinding a study with 2 different dosing schedules.

4.2.5 Rationale for Second Course

Second course therapy is a frequent request from investigators for participants in clinical studies and allows re-treatment with agents from which they have previously benefited. In the KEYNOTE-164 study, an open-label Phase 2 study of pembrolizumab in patients with

previously treated locally advanced unresectable or metastatic MSI-H/dMMR CRC, anti-tumor activity was again observed in 8 of 9 patients following re-exposure to pembrolizumab as part of Second Course treatment.

4.2.6 Rationale for Suicidal Ideation and Behavior Monitoring

Not applicable.

4.3 Justification for Dose

4.3.1 Justification of MK-1308A Dose

The dose composition and schedule of MK-1308A is 25 mg quavonlimab plus 400 mg pembrolizumab to be administered Q6W. This formulation and dosing regimen were chosen after data analyses of 215 participants in the MK-1308-001 study who were given varying dose levels of quavonlimab (25 mg, 75 mg, and 200 mg Q3W or Q6W) and a fixed dose of pembrolizumab (200 mg Q3W). Evaluation of the safety, tolerability, PK, pharmacodynamics, and efficacy data from this part of the study showed that 25 mg quavonlimab Q6W in combination with pembrolizumab Q3W was equally efficacious but safer than the 75 mg and 200 mg quavonlimab dose levels, thus the 25 mg Q6W dose regimen was chosen as the RP2D. Following the selection of the 25 mg Q6W regimen of quavonlimab, the 400 mg Q6W regimen of pembrolizumab was considered appropriate in the development of the pembrolizumab + quavonlimab fixed-dose coformulation (MK-1308A), given the approval of this regimen of pembrolizumab as a safe and efficacious alternative to the 200 mg Q3W regimen. Preliminary PK data collected from 29 participants in the MK-1308-001 study who were treated with MK-1308A showed similar exposures of quavonlimab compared with sequential administration and coadministration of quavonlimab and pembrolizumab. Further, the observed 400 mg Q6W pembrolizumab concentration data in combination with 25 mg Q6W quavonlimab are consistent and within the range of the simulated pembrolizumab monotherapy data at the same dose using the reference population PK model created from 2993 subjects. Analysis of ADA impact on the PK exposure of quavonlimab in combination with pembrolizumab to date show that anti-quavonlimab antibodies do generally reduce quavonlimab exposures in subjects who are ADA positive with higher S/N generally causing lower exposure. Pembrolizumab ADA formation has no impact on exposures of pembrolizumab in combination with quavonlimab. Details regarding PK and ADA data may be found in the quavonlimab, MK-1308A, and pembrolizumab IBs.

It is reasonable to expect the PK of quavonlimab to be consistent with that of other humanized mAbs that typically have a low clearance and a limited volume of distribution. Using a population PK model of ipilimumab, distribution of exposures from the 25 mg quavonlimab fixed-dose considerably overlap that obtained with the 0.3 mg/kg weight-based ipilimumab dose and exposures from the 75 mg quavonlimab fixed dose considerably overlap those obtained with the 1.0 mg/kg weight-based ipilimumab dose [Feng, Y., et al 2014]. Similar to pembrolizumab, a fixed-dose regimen of quavonlimab is expected to reduce complexity in the logistical chain at treatment facilities and reduce waste. The goal in introducing the lower doses of 25 mg quavonlimab at the schedule of Q6W is to determine if a similar response rate can be achieved at lower doses, which would be expected to result in a

reduction in immune-related toxicities. Details regarding specific benefits and risks for participants participating in this clinical study may be found in the quavonlimab, MK-1308A, and pembrolizumab IBs and informed consent documents.

The rationale for coformulation proposed to be evaluated in this study is to provide a simpler regimen in a single vial to support a more convenient dosing paradigm that is less prone to medication errors and can be widely used in multiple clinical settings. Additional information on coformulation is provided in Section 2.2.1.6.

4.3.2 Justification of Pembrolizumab Dose

The planned dose of pembrolizumab monotherapy for this study is 400 mg Q6W.

The 400 mg Q6W dosing regimen of pembrolizumab is approved for adult indications.

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on M&S analyses, given the following rationale.

- PK simulations demonstrating that in terms of pembrolizumab exposures:
  C_{avg} (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

  Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of participants.

  Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.

- Exposure-response for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

When administered in combination with MK-4830 (Section 4.3.5), the planned dose of pembrolizumab is 200 mg Q3W.

The dosage of pembrolizumab for participants who received Q3W dosing in closed arms and who elect to transition to pembrolizumab monotherapy is 200 mg Q3W.

4.3.3 Justification of MK-4280A Dose

The planned dose of the coformulated MK-4280A is 800 mg favezelimab and 200 mg pembrolizumab Q3W.

Preliminary PK profiles of favezelimab exposures suggest that target receptor-mediated clearance (reflecting target engagement of membrane LAG-3) of favezelimab was more likely to stay saturated at ≥700 mg dose compared with lower doses considering PK C_{trough} variability observed. Additionally, efficacy data from a randomized dose-finding study in participants with gastric cancer in MK-4280-001 suggested possible trend toward better efficacy at higher doses. Favezelimab given alone and in combination with pembrolizumab has been tolerable at all dose levels tested from 7 mg to 800 mg with no clear dose dependence in the type or frequency of AEs. For more detailed information, please refer to the MK-4280/MK-4280A IB. Therefore, based on the totality of preliminary data accumulated so far, the Sponsor has elected 800 mg dose of favezelimab in combination with 200 mg pembrolizumab for this study.

4.3.4 Justification of MK-7684A Dose

The planned dose of the coformulated MK-7684A is 200 mg vibostolimab and 200 mg pembrolizumab Q3W.

PK data from Study MK-7684-001 in 323 participants across tumor types indicate that observed PK parameters were generally similar across tumor types. Observed PK profiles of vibostolimab suggest that target-mediated clearance of vibostolimab is saturated at the 200 mg, 210 mg, and 700 mg doses. The PK of vibostolimab is generally consistent with that of other humanized mAbs, which typically have low CL and a limited Vc [Dirks, N. L. and Meibohm, B 2010] [Dostalek,M., et al 2012] [Keizer,R.J., et al 2010]. As with other mAbs, body weight was found to be related to vibostolimab CL and Vc parameters, but the relationship was weak for both parameters. As such, this supports that fixed dosing would provide better control of PK variability than body weight-based dosing [Bai,S., et al 2012] [Hendrikx, J. J. M. A., et al 2017].

Available clinical safety data indicated that vibostolimab is tolerable at doses up to and including 700 mg, both when used as monotherapy and in combination with pembrolizumab. No DLTs were observed at any of the vibostolimab doses tested either as monotherapy or in combination with pembrolizumab during the dose escalation and confirmation portion of Study MK-7684-001, and the MTD was not reached.

Clinical activity was observed at the 200/210-mg and the 700-mg dose levels of vibostolimab both during the dose escalation and confirmation portion of Study MK-7684-001 in participants with advanced solid tumors of all types and during the dose-expansion portion, particularly in PD-1/PD-L1 inhibitor treatment-naïve participants with NSCLC, ovarian cancer, breast cancer, and cervical cancer treated with vibostolimab in combination with pembrolizumab.

The 200 mg and 700 mg doses were compared in a randomized dose-finding cohort of participants with anti-PD-1/PD-L1 treatment-naïve cervical cancer in MK-7684-001 Part B. Exploratory analysis of exposure versus best change in tumor size (based on preliminary data from 63 participants) shows a flat relationship, suggesting that 200 mg is at the plateau of the exposure-efficacy relationship.

Overall, the totality of data, including lack of a clinically meaningful effect of body weight on PK, consistency of PK across indications and a flat dose-exposure-tumor size response relationship support that a fixed-dose of 200 mg Q3W is an optimal dose for vibostolimab in combination with 200 mg pembrolizumab.

4.3.5 Justification of MK-4830 Dose

The planned dose for MK-4830 is 800 mg Q3W.

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 was determined to be MK-4830 800 mg Q3W for use as monotherapy and in combination with pembrolizumab.

The safety of MK-4830, pembrolizumab, and carboplatin/pemetrexed combination therapy is also being evaluated in 1L NSCLC participants in Study MK-4830-001. As of 15-MAR-2021, no DLTs were reported and there were no safety findings that would preclude continued evaluation of MK-4830 800 mg Q3W in combination with pembrolizumab and carboplatin/pemetrexed.

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 (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

The Sponsor estimates that the study will require approximately 60 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

Upon study completion, participants are discontinued and may be enrolled in an extension study, if available.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Participants with dMMR/MSI-H Stage IV CRC, who have measurable disease per RECIST 1.1 as assessed by the site and verified by BICR, and who are either chemotherapy refractory (Cohort A) or have received no systemic treatment for metastatic disease (Cohort B), will be enrolled in this study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age, race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has a histologically confirmed diagnosis of Stage IV CRC adenocarcinoma (as defined by AJCC version 8).
2. Has locally confirmed dMMR/MSI-H.

   Note: Participants diagnosed as dMMR/MSI-H via NGS sequencing should have confirmation via IHC or PCR.
   Note: Subjects participating in the study in France will not be enrolled into Cohort B. They must meet the criteria for Cohort A only for enrollment.

Cohort A:

3. Has been previously treated for their Stage IV dMMR/MSI-H CRC and radiographically progressed on or after or could not tolerate standard treatment, which must include ALL of the following agents if approved and locally available in the country where the participant is randomized:

   Note: Adjuvant chemotherapy counts as prior systemic therapy if there is documented disease progression within 6 months of chemotherapy completion.
   Note: A participant who has withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study. If a participant is determined to be intolerant to a prior line of therapy, the participant must have had a minimum of 2 cycles of that therapy unless discontinuation was due to a life-threatening toxicity.

   a. Fluoropyrimidine, irinotecan and oxaliplatin.

      Note: Capecitabine is acceptable as equivalent to fluorouracil in prior therapy (XELOX/CAPOX and XELIRI are considered equivalent to FOLFOX and FOLFIRI, respectively).
      Note: Participants who have previously received fluoropyrimidine, oxaliplatin, and irinotecan as part of the same and only chemotherapy regimen, eg, FOLFOXIRI or FOLFIRINOX, may participate in the study.

   b. With or without an anti-VEGF monoclonal antibody (eg, bevacizumab)
   c. At least one of the anti-EGFR monoclonal antibodies (cetuximab or panitumumab) for RAS WT participants with left-sided tumors. Prior EGFR therapy is optional for patients with right sided RAS WT tumors.

      Note: For participants with ctDNA RAS mutant but RAS mutation negative in tissue, enrollment into the study before anti-EGFR administration is allowed.

Cohort B:

4. Has untreated Stage IV dMMR/MSI-H CRC with no prior chemotherapy or immunotherapy for this disease.

   NOTE: Participants who have received adjuvant chemotherapy and have documented disease progression within 6 months of chemotherapy completion will not be eligible.

Demographics

5. Is male or female and at least 18 years of age at the time of providing documented informed consent.
6. Has a life expectancy of at least 3 months.
7. Has ECOG Performance Status of 0 to 1 at Screening and within 3 days before Cycle 1 Day 1 treatment.

Female Participants

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

- Not a WOCBP

OR

- A WOCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for a urine test or 72 hours for a serum test before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6. See country-specific requirements in Appendix 7.
  - Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.

Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

9. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR. See country-specific requirements in Appendix 7.

Additional Categories

10. Have measurable disease per RECIST 1.1 as assessed by the site and verified by BICR. Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.

11. Submit an archival (within 5 years of Screening) or newly obtained tumor tissue sample that has not been previously irradiated; FFPE blocks are preferred to slides. If a sufficient specimen does not exist, the participant must be willing to undergo a core or excisional biopsy during Screening. Newly obtained biopsies are preferred to archived tissue. For Cohort A, samples may predate chemotherapy. For Cohort B, the specimen may predate adjuvant chemotherapy (this cohort will have had no therapy for metastatic disease).
12. Have adequate organ function as defined in the following table (Table 4). Specimens must be collected within 72 hours before the start of study intervention.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation*	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard/per local regulatory requirements.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific interventions.

*Coagulation tests do not need to be repeated at C1D1, unless clinically indicated.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Prior/Concomitant Therapy

1. Has received prior therapy with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, PD 1, CTLA-4, OX-40, CD137, PD-L1, ILT-4, LAG-3, TIGIT).
2. Has received prior systemic anticancer therapy including investigational agents within 4 weeks before the first dose of study intervention.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

3. If the participant had a surgery and they have not recovered adequately from the procedure and/or any complications from the surgery before starting study intervention.
4. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
5. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Note: Killed vaccines are allowed. Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

6. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.

   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic Assessments

7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication.
8. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, colon polyps, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

9. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (Note: The repeat imaging should be performed during study screening.), clinically stable and without requirement of steroid treatment for at least 14 days before the first dose of study intervention.
10. Has severe hypersensitivity (≥Grade 3) to pembrolizumab, quavonlimab, favezelimab, vibostolimab, MK-4830, and/or any of their excipients.
11. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
    Exception: Participants with a history of inflammatory bowel disease (eg, Crohn's disease or ulcerative colitis) may not participate, regardless of treatment history.
12. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
13. Has a history of acute or chronic pancreatitis.
14. Has neuromuscular disorders associated with an elevated creatine kinase (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
15. Has urine protein ≥1 g/24h.

    Note: Participants with proteinuria >2+ (≥100 mg/dL) on urine dipstick or urinalysis testing will undergo 24-hour urine collection for quantitative assessment of proteinuria.
16. Has an active infection requiring systemic therapy (eg, tuberculosis, known viral or bacterial infections, etc.).

    Note: No testing for active infections are required unless mandated by local health authority. See country-specific requirements in Appendix 7.
17. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority. See country-specific requirements in Appendix 7.
18. Concurrent active Hepatitis B (defined as HBsAg positive and/or detectable HBV DNA) and Hepatitis C virus (defined as anti-HCV Ab positive and detectable HCV RNA) infection.

    Note: Hepatitis B and C screening tests are not required unless:
    - Known history of HBV and HCV infection
    - As mandated by local health authority
19. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study intervention administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.
20. Has present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks before randomization/allocation.

21. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
22. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

23. Has had an allogenic tissue/solid organ transplant.

5.3 Lifestyle Considerations

Approved contraceptive methods may be found in Appendix 5.

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required. Refer to Appendix 7 for country-specific requirements.

5.3.3 Activity Restrictions

No restrictions are necessary.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently allocated in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail Screening may be rescreened once for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention 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 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 intervention(s) to be used in this study are outlined in Table 5.

All products indicated in Table 5 will be provided centrally by the Sponsor.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

Table 5 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Cohorts A and B: Pembrolizumab monotherapy	Active Comparator	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	400 mg	IV Infusion	Q6W up to 17 doses	Comparator	IMP	Centrally by Sponsor
Cohorts A and B: MK-1308A	Experimental	MK-1308A	Biological/Vaccine	Solution	quavonlimab 25 mg + pembrolizumab 400 mg/ 17.5 mL vial	25 mg/ 400 mg	IV Infusion	Q6W up to 17 doses	Test Product	IMP	Centrally by Sponsor
Cohort B: MK-4280A	Experimental	MK-4280A	Drug	Solution	20 mg/mL favezelimab + 5 mg/mL pembrolizumab for a total of 25 mg/mL	800 mg MK-4280 + 200 mg MK-3475	IV Infusion	Q3W up to 35 doses	Test Product	IMP	Centrally by Sponsor
Cohort B: MK-7684A	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 10 mg/mL + pembrolizumab 10 mg/mL	200 mg MK-7684 + 200 mg MK-3475	IV Infusion	Q3W up to 35 doses	Test Product	IMP	Centrally by Sponsor

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Cohort B: MK-4830 + Pembro-lizumab	Experimental	MK-4830 + Pembro-lizumab	Biological/Vaccine	Solution	MK-4830 50 mg/mL + pembrolizumab 25 mg/mL	800 mg MK-4830 + 200 mg MK-3475	IV Infusion	Q3W up to 35 doses	Test Product	IMP	Centrally by Sponsor
Cohort B: Participants who received Q3W dosing in closed arms	Active Comparator	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	200 mg	IV Infusion	Q3W up to a total of 35 doses including doses received as part of closed arm	Comparator	IMP	Centrally by Sponsor or locally

AxMP = auxiliary medicinal product; EEA =European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product; Q3W= every 3 weeks; Q6W= every 6 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 differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note: MK-4830 will be administered 30 minutes after completion of pembrolizumab infusion. MK-4830 will be administered as an IV infusion over 30 minutes.

6.1.1 Treatment

6.1.1.1 Initial Treatment or First Course

The Initial Treatment or First Course of MK-1308A or pembrolizumab monotherapy consists of up to 17 treatments of Q6W therapy. The Initial Treatment or First Course of MK-4280A, MK-7684A, or MK-4830 plus pembrolizumab consists of up to 35 treatment cycles of Q3W therapy. Note: The number of treatments is calculated starting with the first dose.

Participants may be eligible for Second Course described in Section 6.1.1.2.

In the event of a study arm being closed, the Sponsor may offer investigators the option of continuing study treatment with pembrolizumab monotherapy or continuing the assigned study treatment to participants who are receiving clinical benefit. At implementation of Amendment 05, the following treatment arms are considered closed: Cohort B: MK-4280A, Cohort B: MK-7684A, and Cohort B: MK-4830+pembrolizumab.

As of the Investigator Letter dated 16-DEC-2024, participants who were receiving MK-4280A were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy, and participants who were receiving MK-7684A were discontinued from that study therapy and offered the option to transition to pembrolizumab monotherapy. As per the Investigator Letter dated 25-SEP-2023, the MK-4830+pembrolizumab arm was closed to enrollment; all ongoing participants were offered the option to continue study therapy until treatment completion or transition to pembrolizumab monotherapy. For participants who elect to transition to pembrolizumab monotherapy, the dosage would be 200 mg Q3W up to a total of 35 doses including doses received as part of closed arm.

Participants in closed arms with access to approved SOC (eg, immunotherapy, chemotherapy, targeted therapy) should be considered for discontinuation from the study. Participants in closed arms who are benefiting from pembrolizumab monotherapy, but unable to access it as SOC outside the study, may continue on study and receive treatment with pembrolizumab monotherapy until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.

6.1.1.2 Second Course

Participants in open arms who have SD, PR, or CR may be eligible for up to an additional 9 cycles of Q6W therapy with MK-1308A or pembrolizumab monotherapy if there is BICR-verified radiographic disease progression by RECIST 1.1 after Initial Treatment or First Course has been completed or stopped for confirmed CR. Participants in closed arms who have SD, PR, or CR may be eligible for up to an additional 17 cycles of pembrolizumab monotherapy (200 mg Q3W) if there is radiographic disease progression by RECIST 1.1 after Initial Treatment or First Course has been completed or stopped for confirmed CR. Any participant who has already begun Second Course treatment with MK-4280A or

MK-4830+pembrolizumab at the time of arm closure will be able to complete treatment as planned. This retreatment is the Second Course of this study.

Participants may enter the Second Course if all of the following criteria are met:

1. The participant received MK-1308A, pembrolizumab, MK-4280A, MK-7684A or MK-4830 plus pembrolizumab
2. No new anticancer treatment was administered after the last dose of study intervention
3. The participant meets all of the inclusion criteria and none of the exclusion criteria
4. The study is ongoing

An objective response or disease progression that occurs during the Second Course will not be counted as an event for the primary analysis of either endpoint in this study.

Second Course treatment should remain the same as the final treatment used in the first course of treatment (eg, a participant last treated on MK-1308A will resume treatment with MK-1308A unless toxicity or arm closure resulted in continuation of study treatment with pembrolizumab monotherapy).

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of the study interventions are provided in the Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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

investigator is responsible for ensuring that a local discard/destruction procedure is documented.

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an IRT system. There are 7 study intervention arms. Participants in Cohort A will be assigned randomly in a 1:1 ratio to MK-1308A or pembrolizumab monotherapy, respectively. Participants in Cohort B will be assigned randomly in a 1:1:1:1:1 ratio to MK-1308A, pembrolizumab monotherapy, MK-4280A, MK-7684A, or MK-4830+pembrolizumab, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factor:

- RAS status (mutant vs WT)

  Note: RAS mutation includes KRAS or NRAS

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

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

Refer to Section 8.1.9 for study intervention administration.

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be

recorded in the source documents and recorded in the CRF. The site should ensure and confirm that the study intervention(s) is(are) administered at the correct dose(s) to the assigned study participant.

Refer to Section 6.6.1 for dose modification and toxicity management for irAEs associated with all investigational agents and for other allowed dose interruptions of all investigational agents.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study and 30 days after end of study intervention. 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.

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Antineoplastics (chemotherapies, vaccines, checkpoint inhibitors, etc.) not specified in this protocol
- Investigational agents other than the study interventions
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study. See country-specific requirements in Appendix 7.
  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 for the purposes listed in Section 6.5.1.

The start of additional anticancer therapies by a participant will be considered by the Sponsor as evidence of PD, and study intervention will be discontinued. These participants should complete all end of treatment assessments and continue to be followed for survival in the follow-up period.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study intervention must be discontinued.

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. All concomitant medications will be recorded on the eCRF including all prescriptions, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

Standard medications routinely administered for surgery (anesthetics, muscle relaxants, IV fluids, etc.) do not need to be recorded. Concomitant medications should be recorded for SAEs/AEs related to surgery.

6.5.1 Systemic Corticosteroid Use

Systemic corticosteroids are permitted in the following situations:

- For treatment of potential irAEs, as indicated in Table 6
- As needed for the prevention of emesis
- Pre-medication for IV contrast allergies
- Short-term oral or IV use in doses >10 mg/day prednisone equivalent is permitted when considered standard of care (eg, for exacerbation of COPD)
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

In addition, the following glucocorticoid use is allowed:

- For topical use or ocular use
- Intraarticular joint use
- For inhalation in the management of asthma or COPD.

6.5.2 Rescue Medications and Supportive Care

Study interventions do not need to be given with pre-medications, though noncorticosteroid pre-medications may be introduced on an as needed basis per investigator discretion.

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.

See country-specific requirements in Appendix 7.

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, reinitiation 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 6.

Table 6 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)
	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
				• 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
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		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

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

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

[a] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal

[c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × 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 (MK-1308A, MK-4280A, MK-7684A), or IO Combinations (MK-4830 plus pembrolizumab)

Pembrolizumab monotherapy, coformulations (MK-1308A, MK-4280A, MK-7684A), or IO combinations (MK-4830 plus pembrolizumab) may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab monotherapy, coformulations (MK-1308A, MK-4280A, MK-7684A), or IO combinations (MK-4830 plus pembrolizumab) associated infusion reactions are provided in Table 7.

Table 7 Pembrolizumab Monotherapy, Coformulations (MK-1308A, MK-4280A, MK-7684A), or IO Combinations (MK-4830 plus pembrolizumab) Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 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 after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing

CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.
Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

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 84 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.

Dose interruptions in response to treatment-related AEs are permitted in order to keep the participant on study medication, when appropriate. Proper documentation of the causality of the study medication is required. Details on the modifications for each study intervention are provided in Table 6.

In cases where the toxicity is attributed to the coformulation, combination or to MK-1308, MK-4280, MK-7684, or MK-4830 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

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

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

6.9.1 Study Site Retention Samples

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the 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 be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study (Section 7.2).

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.

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 6.6.1, 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.
- 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 8.2.1.5 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond PFS disease progression).
- Any progression or recurrence of invasive malignancy, or any occurrence of another malignancy that requires active treatment. An exception should be made for LS participants as noted in Section 4.2.1.1.
- 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.

- Prohibited medication or vaccination required, and agreement between Sponsor, investigator, and participant to discontinue study intervention.

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

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

Refer to Section 8.11.4 for posttreatment follow-up information for participants in closed arms.

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 intervention 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 FBR, are outlined in Section 8.1.10. 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 used for screening or baseline purposes provided the procedures meet 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.

The maximum amount of blood collected from each participant over the duration of the study can be found in the Laboratory Manual or Procedure Document.

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.

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, site personnel will add the allocation number to the participant identification card.

The participant ID 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

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

8.1.5 Oncologic Medical History

The investigator or qualified designee will obtain specific medical history of the participant's cancer under study. This information will include, but is not limited to, date of diagnosis, stage, histology, MSI/MMR status, RAS (KRAS and NRAS) and BRAF mutation status, location(s) of primary lesions, and location(s) of metastases, if applicable.

For MSI/MMR status, the history will note the method of testing used (ie, PCR, IHC) and the result of the test (eg, MMR gene expression loss or number of allelic shifts on PCR).

The MSI/MMR status must be known prior to enrollment and the participants must be dMMR/MSI-H. If not known, MSI/MMR status must be performed by the sites' local laboratory using one method ie, IHC or PCR prior to enrollment.

Colorectal tumor MMR status is determined by IHC, while MSI status is determined by PCR. Tumors are classified as dMMR in the absence of at least 1 of 4 MMR proteins (MLH1/MSH2/MSH6/PMS2) or MSI-H when at least 2 allelic shifts among 5 analyzed microsatellite loci are detected.

RAS mutation status must also be known for all participants prior to enrollment. If not known, RAS mutation status testing must be performed by the site locally during screening and confirmed prior to participant allocation.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

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

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up Visit should be recorded.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.8 Assignment of Treatment/Randomization Number

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

A single participant cannot be assigned more than 1 allocation number.

8.1.9 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or an appropriately qualified designee according to the specifications within the Pharmacy Manual.

Study intervention should begin within 3 days of intervention allocation.

8.1.9.1 Timing of Dose Administration

Study treatment should be administered within 3 days of Day 1 of Cycle 1 and then up to 3 days before or after the scheduled Day 1 of each cycle after all procedures and assessments are completed according to the SoA (Section 1.3, Table 1, Table 2, and Table 3).

All study treatments will be administered using a 30-minute IV infusion. 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 between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

For participants in Cohort B who are receiving MK-4830+pembrolizumab, the pembrolizumab infusion should be administered first. MK-4830 will then be administered 30 minutes after the completion of the pembrolizumab infusion.

8.1.10 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 as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the End of Treatment 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.

Refer to Section 8.11.4 for posttreatment follow-up information for participants in closed arms.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. 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 FBR 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 before 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.

If 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.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

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

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.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant completes or is withdrawn from the study or goes into Survival Follow-up. The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans by CT for the chest, abdomen, and pelvis, 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.

If brain scans are performed, MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain X-rays acquired for correlation, should be submitted to the iCRO.

Other types of medical imaging (such as ultrasound) should not be submitted to the iCRO and will not be included in response assessment.

At Screening, participant eligibility will require radiographic documentation of at least one lesion that meets the requirements for selection as a target lesion, as defined by RECIST 1.1 assessed by the site and verified by BICR, prior to participant allocation.

All scheduled scans for all study participants will be submitted to the iCRO. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows disease progression, or if it is used to support a response assessment. All scans acquired within the protocol-specified window of time around a scheduled scan visit are to be classified as pertaining to that visit.

When the investigator identifies radiographic progression per RECIST 1.1, BICR will perform expedited verification of radiologic disease progression and the results will be communicated to the study site and the Sponsor via email. In clinically stable participants, imaging will continue until disease progression has been verified by BICR as described in Section 8.2.1.2.

For participants in closed arms, imaging scans should no longer be submitted to the iCRO nor read by BICR. For participants in closed arms who are still on study treatment, deriving clinical benefit, and will continue study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. In closed arms, all imaging as well as relevant objectives and endpoints will be assessed locally.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of allocation. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease per RECIST 1.1.

The screening scans must be submitted to the iCRO to verify eligibility criteria have been met before allocation.

Tumor scans performed as part of routine clinical management are acceptable for screening if they are of acceptable diagnostic quality and performed within 28 days of allocation and can be assessed by the iCRO.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 9 weeks (63 days ±7 days) from the date of allocation. Subsequent tumor scans should be performed every 9 weeks (63 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 and verified by the BICR, for participants in open arms, or until the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular 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 or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

For participants who have surgery with curative intent during the study, scans must be performed at a minimum of no less than 4 weeks after surgery and no more than 8 weeks prior to the next treatment cycle. The last set of scans prior to restart of treatment will be used to establish a new baseline of tumor burden. Subsequent scans will be compared to this new baseline and the visit responses will be limited to PD, non-PD, or NE (not evaluable); these new post-operative images will be assessed every 9 weeks (63 days ± 7 days) from the

new baseline scan date until disease progression is assessed by the site and verified by BICR or initiation of a new anticancer treatment.

While off study intervention, participants who undergo surgical resection of visible disease may demonstrate disease progression in non-surgical sites. In this instance, disease progression might not necessarily reflect resistance to study intervention. Accordingly, participants who develop isolated lesion/tumor growth post-operatively (eg, while off study intervention) may resume the previously assigned study intervention. The investigator must assess overall clinical benefit to the participant and consult the Sponsor prior to resuming study intervention.

Refer to Section 8.2.1 for imaging information for participants in closed arms.

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 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 allocation (refer to Section 8.2.1.2).

Scans are to be continued until one of the following conditions are met:

- disease progression as defined by RECIST 1.1 verified by BICR
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

Refer to Section 8.11.4 for posttreatment follow-up information for participants in closed arms.

8.2.1.4 Second Course (Retreatment) Tumor Scans

Tumor scans must be performed within 28 days before restarting study intervention.

If disease progression has been verified by BICR (required only for participants in open arms) for the First Course, the Second Course may be initiated. The disease progression scan may be used as the Second Course baseline scan if performed within 4 weeks prior to dosing and meets scan standards.

The first scan should be performed at 9 weeks (63 days ±7 days) after restarting study intervention. Subsequent tumor scans are to be performed every 9 weeks (63 days ±7 days) or more frequently, if clinically indicated.

Scans are to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, completion of Second Course or notification by the Sponsor, whichever occurs first.

If participants discontinue study intervention, tumor scans are to be performed at 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 every 9 weeks (63 days ±7 days) until either the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

Response assessments and progressive disease are determined by investigator assessment.

The only Second Course scan to be provided to the iCRO is the baseline scan if it is the final scan for the Initial Treatment or First Course.

Refer to Section 8.2.1 for imaging information for participants in closed arms.

8.2.1.5 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.

Upon investigator-assessed disease progression, for participants in open arms, the indicative scans are to be submitted immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
  - resume imaging per protocol schedule (≥4 weeks to next scan)
  - send scans to iCRO
  - continue local assessment
  - do not change investigator assessment of progression

  - if subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification

- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

If disease progression is verified, the process continues as follows:

- investigator judgement 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

- obtain scans locally per original protocol schedule

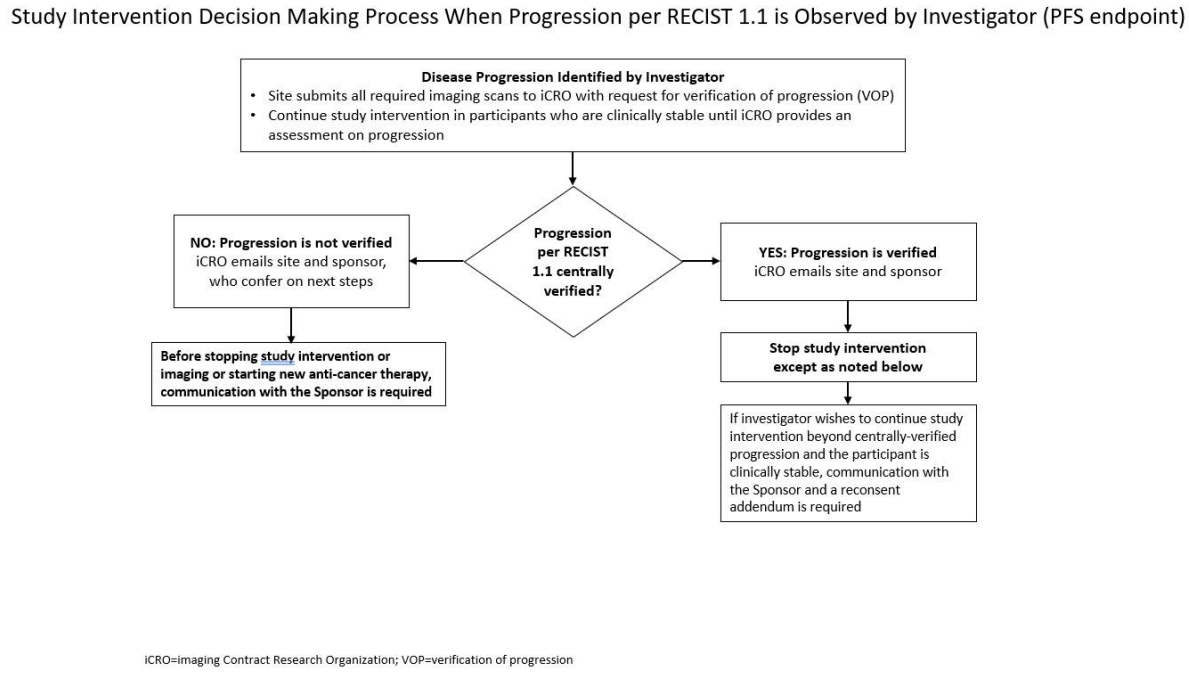
- do not send scans to iCRO

Figure 2 illustrates the study intervention decision process involving verification of disease progression for participants.

- 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

Refer to Section 8.2.1 for imaging information for participants in closed arms.

Figure 2 Study Intervention Decision Making Process When Progression per RECIST 1.1 is Observed by Investigator (PFS Endpoint)



8.2.2 Patient-reported Outcomes

CCI [redacted]

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 or Procedure Document.

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

Participants in closed arms who complete study treatment (including Second Course, if applicable) or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required Safety Follow-up Visit.

Participants in closed arms remaining on study should continue to be monitored in the study through the AE reporting period (Section 8.4).

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee (consistent with local requirements) will perform a complete physical examination during the screening period per institutional standard. Height and weight will also be measured and recorded. Clinically significant abnormal findings should be recorded as medical history.

Time points for full physical exams are described in Section 1.3. After the first dose of 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.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee (consistent with local requirements) will perform a brief directed physical examination (per institutional standard) as clinically indicated before study intervention administration. 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

- Temperature, pulse rate, RR, and BP will be assessed by institutional standard.
- BP and pulse measurements will be assessed per institutional standard with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic BP, and pulse and RR.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures pulse rate, QRS, and QT intervals.

8.3.4 Performance Assessments

8.3.4.1 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc.) with Grades 0 to 5.

The investigator or qualified designee will assess ECOG status (see Appendix 8) at Screening, before the administration of each dose of study intervention, at the End of Treatment Visit, and at the 30 day Safety Follow-up Visit, as specified in the SoA (Section 1.3).

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the 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 or Procedure Document 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 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 Laboratory Manual or Procedure Document. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

8.3.5.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis, Etc.)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2 along with tests for thyroid function, cortisol, and ACTH.

8.3.5.2 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 within 24 hours (urine) or 72 hours (serum) prior to the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation.

8.3.6 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted prior to every cycle during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

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

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

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, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1, or 30 days after 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 specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former 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 the investigator 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 8.

Table 8 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer 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: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Potential DILI events meeting biochemical criteria of Hy's Law (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report - regardless of suspected etiology - to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor
ECI (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – requires regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
AE=adverse event; DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; OME=other important medical event; SAE=serious adverse 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. SAEs and other reportable safety events, including potential DILI events meeting biochemical criteria of Hy's Law, 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). The investigator will also make every attempt to follow nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward 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 SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

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.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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 ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest

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

ECIs for this study include:

All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential DILI events are defined as:

- An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and,
- An elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and,
- At the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN,

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 may require 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).

Additional ECIs for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

8.5 Treatment of Overdose

For this study, an overdose of MK-1308A will be defined as any dose of 62.5 mg / 1000 mg MK-1308A or greater.

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

For this study, an overdose of MK-4280A will be defined as any dose of 1600 mg / 400 mg MK-4280A or greater.

For this study, an overdose of MK-7684A will be defined as any dose of 600 mg / 600 mg MK-7684A or greater.

For this study, an overdose of MK-4830 will be defined as any dose of 1200 mg of MK-4830 or greater.

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

8.6 Pharmacokinetics

CCI

[redacted]

8.6.1 Blood Collection for PK

CCI

[redacted]

8.6.2 Blood Collection for ADA

CCI

[redacted]

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

CCI

[redacted]

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the Laboratory Manual or Procedure Document.

For participants in closed arms, biomarker samples will no longer be collected.

8.8.1 Planned Genetic Analysis Sample Collection

CCI

[redacted]

8.9 Future Biomedical Research Sample Collection

CCI

[redacted]

8.10 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:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation through 90 days after cessation of study intervention, or 30 days

after cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

For participants in closed arms, data on medical resource use and health economics will no longer be collected.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

Refer to Section 6.1.1 for study intervention information, Section 8.2.1 for imaging information, Section 8.2.2 for PRO collection information, Section 8.3 for safety monitoring information, Section 8.6 for PK/ADA sample collection information, Section 8.8 for biomarker sample collection information, and Section 8.11.4 for posttreatment follow-up information for participants in closed arms.

8.11.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant provides documented informed consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention.

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

8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

Cohort B participants on Q6W study drug dosing schedule will have a Day 22 visit at each 6-week cycle and undergo assessments as listed in the SoA (Section 1.3).

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

Participants who discontinue study treatment due to disease progression or start of a new anticancer therapy will have Safety Follow-up and then proceed directly to Survival Follow-up as described in Section 8.11.4.3.

The End of Treatment Visit should occur at the time study intervention is discontinued for any reason. If the End of Treatment Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the End of Treatment Visit procedures and any additional Safety Follow-up procedures should be performed. Additional details regarding participant treatment discontinuation can be found in Section 7.1.

8.11.4 Posttreatment Visits

Participants in closed arms who complete study treatment (including Second Course, if applicable) or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required Safety Follow-up Visit. There will be no follow-up for survival status. Participants in closed arms currently in Survival Follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local SOC. Participants in closed arms currently in Efficacy Follow-up will be imaged as per local SOC with no central review. Standard safety reporting should, however, continue as applicable. Participants in closed arms remaining on study should continue to be monitored in the study through the AE reporting period (Section 8.4).

8.11.4.1 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.

Participants who are eligible for retreatment with MK-1308A or pembrolizumab monotherapy may have up to 2 safety follow-up visits: 1 after the Initial Treatment or First Course and 1 after the Second Course.

8.11.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up and should be assessed by continued tumor imaging every Q9W 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, or if the participant begins retreatment as detailed in Section 6.6. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment according to the criteria in Section 6 will move from Efficacy Follow-up to Second Course when they experience disease progression. Details are provided in the SoA (Section 1.3) for retreatment.

8.11.4.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed 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 End of Treatment Visit and/or Safety Follow-up Visit (whichever is last).
2. For participants who completed assessments in Efficacy Follow-up due to progressive disease, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.5 Vital Status

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

If a participant withdraws consent, vital status (survival information) may be obtained by review of public records, in accordance with local regulations. If a participant is lost to follow-up, vital status (survival information) can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

CCI [redacted]

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase 2, Multicenter, Multi Arm, Study to Evaluate MK-1308A (Coformulated quavonlimab (MK-1308)/pembrolizumab) Versus Other Treatments in Participants with Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Cancer: (MK-1308A-008)
Treatment Assignment	Cohort A: Approximately CCI participants will be randomized in a 1:1 ratio between 2 treatment groups: MK-1308A arm; Pembrolizumab monotherapy arm. Cohort B: Approximately CCI participants will be randomized in a 1:1:1:1:1 ratio among 5 treatment groups: MK-1308A, MK-4280A, MK-7684A, MK-4830+pembrolizumab and pembrolizumab monotherapy arm. Stratification factor for Cohorts A and B is RAS status (mutant vs WT). This is an open-label study.
Analysis Populations	Efficacy: ITT population Safety: APaT
Primary Endpoint(s)	ORR as assessed by BICR per RECIST 1.1
Key Secondary Endpoint(s)	DOR as assessed by BICR per RECIST 1.1
Statistical Methods for Key Efficacy Analyses	For each cohort: The stratified M&N method [Miettinen, O. and Nurminen, M. 1985] will be used for comparison of ORR between arms. The point estimate of ORR will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. The nonparametric Kaplan-Meier method will be used to estimate the DOR (if sample size permits).

Statistical Methods for Key Safety Analyses	Cohorts A and B: For analyses in which 95% CIs will be provided for between treatment differences in the percentage of participants with events, these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	CCI [redacted]
Multiplicity	CCI [redacted]
Sample Size and Power	The planned sample size is approximately 320 participants. Cohort A: The planned sample size is approximately CCI [redacted] participants. Cohorts B: The planned sample size is approximately CCI [redacted] participants. CCI [redacted]

9.2 Responsibility for Analyses/In-house Blinding

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

This study is being conducted as an open-label study, ie, participant, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

Primary

- **Objective Response Rate**

  The ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

Secondary

- **Duration of Response**

  For participants who demonstrate confirmed CR or PR, duration of response is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

- **Progression-Free Survival**

  The PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 or death due to any cause, whichever occurs first.

- **Overall Survival**

  OS is defined as the time from randomization to death due to any cause.

- **Objective Response Rate**

  The ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by the investigator.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, SAEs, fatal AEs, laboratory tests, and vital signs. Furthermore, specific events will be collected and designated as ECIs as described in Section 8.4.7.

9.4.3 PRO Endpoints

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the primary population for the analysis of efficacy data in this cohort. The ITT population consists of all randomized participants. Participants will be analyzed in the treatment arm to which they are randomized. Details of the approach to handling missing data are provided in Section 9.6.1.5.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population for each cohort, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 PRO Analysis Populations

CCI [redacted]

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

Efficacy analyses will be conducted for each cohort separately. The stratification factor used for randomization (see Section 6.3.2) will be applied to all stratified analyses.

9.6.1.1 Objective Response Rate (ORR)

The stratified M&N method [Miettinen, O. and Nurminen, M. 1985] will be used for comparison of the ORR between arms.

The point estimate of ORR will be provided by treatment group and cohort, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

9.6.1.2 Duration of Response (DOR)

The nonparametric Kaplan-Meier method will be used to estimate the DOR curve if sample size permits, and median estimate from the Kaplan-Meier curve will also be provided. Only the subset of participants who show a confirmed CR or PR will be included in this analysis.

Censoring rules for DOR are summarized in Table 9.

Table 9 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥ 2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥ 2 missed adequate disease assessments and new anticancer therapy, if any	Censor (non-event)
Death or progression after ≤ 1 missed disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)

DOR=duration of response; PD=progressive disease.
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

9.6.1.3 Progression-Free Survival (PFS)

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve, and median estimate from the Kaplan-Meier curve will also be provided. The stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate will be reported.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a PD event.

For PFS analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer therapy will be censored at the last disease assessment prior to the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the PFS analysis are summarized in Table 10.

Table 10 Censoring Rules for PFS

Situation	Primary Analysis
PD or death documented after ≤ 1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death
Death or progression immediately after ≥ 2 consecutive missed disease assessments, or after new anticancer therapy	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anticancer therapy, if any
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment
PD=progressive disease; PFS=progression-free survival.	

9.6.1.4 Overall Survival (OS)

The nonparametric Kaplan-Meier method will be used to estimate the survival curve, and median estimate from the Kaplan-Meier curve will also be provided. For Cohort A, a stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate will be reported.

Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.5 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 11.

Table 11 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per RECIST 1.1 by BICR	Stratified Miettinen and Nurminen method Summary statistics with 95% CI using Exact method based on binomial distribution	Cohorts A and B: ITT	Participants with missing data are considered non-responders
Secondary Analyses			
DOR per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	Cohorts A and B: All Responders	Censored according to rules in Table 9
PFS per RECIST 1.1 by BICR	Estimation: Stratified Cox model with Efron's tie handling method Summary statistics using Kaplan-Meier method	Cohorts A and B: ITT	Censored according to rules in Table 10
OS	Estimation: Stratified Cox model with Efron's tie handling method Summary statistics using Kaplan-Meier method	Cohorts A and B: ITT	Censored at the date participant last known to be alive

BICR=blinded independent central review; CI=confidence interval; DOR=Duration of Reponses; ITT=intention-to-treat population; M&N=Miettinen & Nurminen; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests and vital signs. Safety analyses will be conducted for each cohort separately.

The analysis of safety results will follow a tiered approach (Table 12). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on observed proportions of participants with an event.

Tier 1 Events

CCI [redacted]

CCI [redacted]

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the M&N method, an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

For continuous measures such as changes from baseline in laboratory and vital sign parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 12 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
CCI [redacted]			

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

CCI [redacted]

9.6.4 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized for each cohort either by descriptive statistics or categorical tables.

9.7 Interim Analyses

CCI [redacted]

CCI [redacted]

9.8 Multiplicity

CCI [redacted]

9.9 Sample Size and Power Calculations

The planned sample size is approximately 320 participants.

CCI [redacted]

CCI

[redacted]

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for ORR will be estimated and plotted within each category of the following subgroup variables:

CCI

[redacted]

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of cycles and number of days for which the participant receives the study intervention for each cohort. Summary statistics will be provided on the extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to conducting these trials in compliance with the highest ethical and scientific standards. Trial conduct includes processes from design to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate. 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 MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and 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, randomization, and blinding) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of

stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. The use of innovative digital health technologies will be considered. Factors critical to the quality of the trial should also be identified. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Risks to critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are

intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

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

III. Participant Protection

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

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

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. 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. Informed consents include relevant aspects of the trial, such as trial design, anticipated benefits and risks of medical intervention(s), trial setting, and the potential use of technology. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed.

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record 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 their 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, frequently 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 their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

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 before transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate siDMC will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency (Section 9.7 Interim Analyses) for evidence of adverse effects of study intervention. The siDMC will determine whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

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 ICMJE 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 trials Regulation 536/2014, 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, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. For studies conducted under the EMA Clinical Trials Regulation 536/2014, a summary of the study results will be submitted in compliance with the regulation**.** MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 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 Regulation 536/2014, 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, ICH 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.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

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 (eg, EU CTR: 25 years after the end of the study). 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 15 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. See country-specific requirements in Appendix 7.

Table 15 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices[a]: MCV MCH % Reticulocytes	WBC count with Differential[b]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN[c]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Carbon dioxide (CO_2 or Bicarbonate)	Chloride	Phosphorous
	Creatinine[d]	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting preferred)	Calcium	Alkaline phosphatase	Amylase/Lipase[e]
Routine Urinalysis[f]	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing[g]	• Highly sensitive serum or urine pregnancy test (as needed for WOCBP)			
Screening Only Tests	• PT/INR and aPTT/PTT[h] • FSH (as needed in WONCBP only)[i] • Serology (HIV antibody, HBsAg, and Hepatitis C virus antibody). NOTE: certain ex-US sites require testing for HIV and Hepatitis B and C during screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable.[j]			

Laboratory Assessments	Parameters
Other Tests	• Thyroid function test: TSH, T3/T4, and free T3/T4[k] • Cortisol (collect specimens at the same time of day) and ACTH (ACTH testing is to be done per investigator's discretion) • Serum Tumor Marker (CEA)

ACTH=adrenocorticotropic hormone; ALT=alanine aminotransferase; aPTT= activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C1D1=Cycle 1 Day 1; CEA= carcinoembryonic antigen; DNA= deoxyribonucleic acid; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HBsAg= Hepatitis B surface antigen; HBV=Hepatitis B Virus; HCV=Hepatitis C Virus; INR= international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT= partial thromboplastin time; RBC=red blood cell; RNA= ribonucleic acid; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3/T4= triiodothyronine/ thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

a. Performed only if considered local standard of care.
b. Absolute or % acceptable per institutional standard.
c. Urea is acceptable if BUN is not available as per institutional standard.
d. Glomerular filtration rate (GFR) (measured or calculated) or creatinine clearance can be used in place of creatinine.
e. Obtain lipase and amylase at screening, EOT and 30-day follow-up.
f. If urine dipstick is abnormal, urinalysis must be performed.
g. Perform on WOCBP only 24 hours before first dose. Pregnancy tests must be repeated before every cycle.
h. Performed as part of the screening assessment for all participants and as clinically indicated for participants taking anticoagulants.
i. If necessary, to check menopausal status.
j. HBsAg or HBV DNA. HCV RNA (qualitative) or HCV antibody.
k. Participants may be dosed while thyroid function tests are pending. Free T3/T4 is acceptable when total T3/T4 cannot be determined.

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 includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, 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 preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- 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 considered a reportable event unless it results in hospitalization or death. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

CCI

[redacted]

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 preexisting condition that has not

worsened is not an SAE.) A preexisting 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.
   - All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as an ECI and SAE with OME criteria in the absence of other SAE criteria within 24 hours of learning of the event.

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 time frame as SAEs to meet certain local requirements. Therefore, these events are to be considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not the cancer under 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/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

10.3.6 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 email 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: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

See country-specific requirements in Appendix 7.

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 non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[c,d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This 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. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. 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 specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before 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.

If 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 withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 France-specific Requirements

Participants participating in the study in France will not be enrolled into Cohort B. Therefore, changes that only pertain to Cohort B (as identified) may not be applicable in France.

Section 1.3 Schedule of Activities

Pregnancy testing must be performed at each cycle during treatment, as well as at the end of study treatment and at Safety Follow-up.

10.7.2 Germany-specific Requirements

Section 1.3 Schedule of Activities

Monthly urine pregnancy testing is required during study intervention as well as at the end of study intervention.

Section 5.1 Inclusion Criteria

Inclusion Criterion: The participant has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Section 5.2 Exclusion Criteria

Exclusion Criterion: Participant has a known history of HIV infection. HIV testing is required for participants.

Exclusion Criterion: Hepatitis B and C testing is required for participants.

Section 6.5.2 Rescue Medications and Supportive Care

Live vaccines must not be administered for 90 days after the last dose of study intervention.

Legally Acceptable Representative protocol sections

In order for a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Section 10.2: Clinical Laboratory Tests

TB added to Other Tests.

Section 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Monthly urine pregnancy testing after randomization is required during study intervention, as well as at the end of study intervention and at Safety Follow-up.

10.7.3 South Korea-specific Requirements

Section 5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Alcohol consumption is significantly discouraged due to the known liver toxicities associated with the study treatments.

10.7.4 United Kingdom-specific Requirements

Section 1.3 Schedule of Activities

Monthly urine pregnancy testing is required during treatment, as well as at the end of study treatment, and at Safety Follow-up.

Section 5.1 Inclusion Criteria

Inclusion Criterion: Monthly urine pregnancy testing is required during treatment as well as at the end of study treatment.

Section 6.5 Concomitant Therapy

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention.

Refer to Section 6.5 for details regarding COVID-19 allowance.

Section 10.5 Appendix 5: Contraceptive Guidance

Monthly urine pregnancy testing is required during treatment, as well as at the end of study treatment and at Safety Follow-up.

10.7.5 Estonia-specific Requirements

Section 1.3 Schedule of Activities

Monthly urine pregnancy testing is required during study intervention as well as up to 120 days after the end of study intervention.

Section 6.5.2 Rescue Medications and Supportive Care

Live vaccines must not be administered for 90 days after the last dose of study intervention.

10.8 Appendix 8: Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

[ECOG ACRIN Cancer Research Group 2016]

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
1L	first line of therapy
2L	second line of therapy
Ab	antibody
ADA	antidrug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
ADL	activities of daily living
AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
APaT	all participants as treated
APC	antigen-presenting cells
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BICR	blinded independent central review
BOR	best overall response
BP	blood pressure
BRAF	B-Raf gene
CAPOX	capecitabine and oxaliplatin
C_{avg}	average plasma concentration over the dosing interval
CD155	cluster of differentiation 155
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CD80	cluster of differentiation 80
CD86	cluster of differentiation 86
CFR	Code of Federal Regulations

Abbreviation	Expanded Term
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE (v5.0)	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
dMMR	mismatch repair deficient
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
EEA	European Economic Area
EGFR	epidermal growth factor receptor

Abbreviation	Expanded Term
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQoL 5-dimension, 5-level scale
ESMO	European Society for Medical Oncology
ES-SCLC	extensive-stage small cell lung cancer
EU	European Union
EU CT	European Union Clinical Trial
EU CTR	European Union Clinical Trials Regulation
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act
FDC	fixed-dose combination
FFPE	formalin-fixed, paraffin embedded
FOLFIRINOX	folinic acid, fluorouracil, irinotecan, and oxaliplatin
FOLFIRI	folinic acid, fluorouracil, and irinotecan
FOLFOX	folinic acid, fluorouracil, and oxaliplatin
FOLFOXIRI	folinic acid, fluorouracil, oxaliplatin, and irinotecan
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA-G	human leukocyte antigen-G

Abbreviation	Expanded Term
HR	heart rate
HRQoL	health-related quality of life
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
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
ICSR	Individual Case Safety Report
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IL-10	interleukin-10
ILT4	immunoglobulin –like transcript 4
IMP	investigational medicinal product
IO	immuno-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	response evaluation criteria in solid tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous

Abbreviation	Expanded Term
IVD	in vitro diagnostic
KPS	Karnofsky performance status
KRAS	Kirsten rat sarcoma viral oncogene homolog
LAG-3	lymphocyte activation gene 3
LS	Lynch syndrome
M&N method	Miettinen & Nurminen method
M&S	Modeling and Simulation
mAb	monoclonal antibody
mCRC	metastatic colorectal cancer
MDSC	myeloid-derived suppressor cells
MHC	major histocompatibility complex
MMR	mismatch repair
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next generation sequencing
NK	natural killer
NRAS	neuroblastoma RAS viral oncogene homolog
NSCLC	non–small cell lung cancer
OME	other important medical event
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter

Abbreviation	Expanded Term
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
pMMR	mismatch repair proficient
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
QoL	quality of life
RAS	genes that makes the proteins called KRAS, HRAS, and NRAS
RECIST 1.1	Response Evaluation Criteria In Solid Tumors 1.1
RFS	relapse-free survival
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	respiratory rate
SAE	serious adverse event
SD	stable disease
SHP-1	Src homology 2 domain-containing protein tyrosine phosphatase 1
siDMC	standing internal Data Monitoring Committee
SIM	Site Imaging Manual
SLAB	supplemental laboratory test(s)
SmPC	Summary of Product Characteristics

Abbreviation	Expanded Term
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIL	tumor-infiltrating lymphocyte
TNM	tumor nodes metastasis
TPS	tumor proportion score
Tregs	regulatory T-cells
TRAE	treatment-related adverse event
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
WOCBP	woman/women of childbearing potential
WT	wild-type
XELIRI	capecitabine and irinotecan
XELOX	capecitabine and oxaliplatin
ZAP70	zeta-chain-associated protein kinase

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