Official Protocol Title:	A Phase 2 trial to evaluate the safety and efficacy of vicriviroc (MK-7690) in combination with pembrolizumab (MK-3475) in participants with advanced/metastatic microsatellite stable (MSS) colorectal cancer (CRC)
NCT number:	NCT03631407
Document Date:	07-Aug-2019

Title Page

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Protocol Title: A Phase 2 trial to evaluate the safety and efficacy of vicriviroc (MK-7690) in combination with pembrolizumab (MK-3475) in participants with advanced/metastatic microsatellite stable (MSS) colorectal cancer (CRC)

Protocol Number: 046-02

Compound Number: MK-7690

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	139660

Approval Date: 07-August-2019

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 2	07-AUG-2019	• Clarification of AE/SAE reporting of progression of cancer under study. • Minor clarifications of timepoints and windows of activities and sample collections in the Schedule of Activities
Amendment 1	22-AUG-2018	• Clarification of Grade 3 DLT definition. • Clarification of study intervention dosing sequence. • Clarification of tumor imaging schedule in first year of study.
Original Protocol	28-JUN-2018	• Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

Clarification of AE/SAE reporting of progression of cancer under study, timepoints and windows of activities, and sample collections in the Schedule of Activities.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) Blood for genetic analysis	It is specified that blood for genetic analysis is to be collected at C1D1 predose from all randomized participants only. This is a requirement of the main study and is separate from the future biomedical research consent (as described in Sections 8.9 and 8.10).	This clarifies the collection requirement of blood for genetic analysis at Screening for all randomized participants.
1.3 Schedule of Activities (SoA) Blood for immune profiling (immunophenotyping)	It is specified that 2 distinct samples are to be collected for immunophenotyping with allowable windows for collection: 1 at Screening AND 1 at predose C1D1 to ensure a sample for biomarker analysis is collected AND analyzed at baseline prior to receiving drug. Screening samples must be collected between -28 days to -3 days. During treatment, collect predose samples 30 minutes before dosing on Day 1 of each cycle for Cycles 1, 2, and 4, and every 4 cycles thereafter.	This clarifies the blood collection timepoints and allowable windows during Screening and treatment cycles for immune profiling.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) Serum for pembrolizumab PK	It is specified that the reference timepoint and allowable window for collection of 0.5 h is within 30 minutes from the end of pembrolizumab infusion.	This clarifies the timing and allowable window of the 0.5 h post-dose PK sample collection.
1.3 Schedule of Activities (SoA) Plasma for vicriviroc PK	It is specified that on C1D1 and C2D1, the post-dose vicriviroc PK samples collected at 8 h will have a ±30 minute collection window.	This clarifies the allowable window for the vicriviroc 8 h post-dose sample collection.
1.3 Schedule of Activities (SoA) Blood for Serum Cytokines	It is specified that Screening samples must be collected between -28 days to -3 days, During treatment samples are to be collected predose on Day 1 of each cycle for Cycles 1, 2, and 4, and every 4 cycles thereafter.	This clarifies the blood collection timepoints and allowable windows during Screening and treatment cycles for immune profiling.
1.3 Schedule of Activities (SoA) Archival and/or newly obtained tissue collection	A ±3-day window for collection of the optional on-treatment biopsy is added.	It is specified that collection of the Cycle 3 optional tumor tissue biopsy has a window of ±3 days.
5.1 Inclusion Criteria Criterion #5	It is specified that if submitting unstained cut slides, newly cut slides should be submitted within 7 days after the slides are cut.	This clarifies the timelines for submission of newly cut slides to reduce shipment times and stability issues.
8.1.8 Study Intervention Administration - Vicriviroc	It is specified that during on-site visits, daily morning administration of vicriviroc should be withheld and taken when witnessed by the investigator and/or trial staff. It is also added that the date and time of the last dose of vicriviroc (taken at home) should be documented in the eCRF.	Instructions are added to withhold vicriviroc dosing at on-site visits and to capture vicriviroc dosing date/time prior to clinic visit. This will better define information for PK modeling.

Section # and Name	Description of Change	Brief Rationale
10.3.1 Definition of AE – Events meeting the AE definition	It is specified that progression of the cancer under study is not a reportable event.	This clarifies AE/SAE reporting of progression of cancer under study.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 trial to evaluate the safety and efficacy of vicriviroc (MK-7690) in combination with pembrolizumab (MK-3475) in participants with advanced/metastatic microsatellite stable (MSS) colorectal cancer (CRC)

Short Title: Vicriviroc plus pembrolizumab in advanced/metastatic MSS CRC

Acronym: NA

Hypotheses, Objectives, and Endpoints:

In participants with advanced/metastatic MSS CRC following administration of vicriviroc in combination with pembrolizumab by vicriviroc dosage treatment Arms A and B:

Primary Objectives	Primary Endpoints
- Objective: To evaluate the objective response rate (ORR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).	- Objective response is a confirmed complete response (CR) or partial response (PR).
- Objective: To determine the safety and tolerability.	- Dose-limiting toxicity (DLT) - Adverse event (AE) - Discontinuation of study treatment due to an AE
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate ORR as assessed by the investigator based on modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST) [Seymour, L., et al 2017], progression-free survival (PFS) as assessed by the investigator based on RECIST 1.1 and iRECIST, and overall survival (OS).	- Objective response is a confirmed CR or PR. - PFS is the time from the first dose of study intervention to the first documented disease progression or death due to any cause, whichever occurs first. - OS is the time from the first dose of study intervention to death due to any cause.
- Objective: To evaluate the pharmacokinetics (PK) of vicriviroc.	- PK parameters including AUC in nM·hr, maximum concentration (Cmax) in nM, and trough concentration (Ctrough) in nM

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Colorectal Cancer
Population	Participants with advanced/metastatic MSS CRC
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	None
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 2 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 40 participants will be enrolled.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Levels</th><th>Route of Admin.</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td rowspan="2">Arm A (N = 20)</td><td>Vicriviroc (MK-7690)</td><td>30 mg</td><td>150 mg</td><td>Oral</td><td>QD</td><td>Experimental</td></tr>
<tr><td>Pembrolizumab</td><td>100 mg/vial</td><td>200 mg</td><td>IV infusion</td><td>Q3W</td><td>Experimental</td></tr>
<tr><td rowspan="2">Arm B (N = 20)</td><td>Vicriviroc (MK-7690)</td><td>50 mg</td><td>250 mg</td><td>Oral</td><td>QD</td><td>Experimental</td></tr>
<tr><td>Pembrolizumab</td><td>100 mg/vial</td><td>200 mg</td><td>IV infusion</td><td>Q3W</td><td>Experimental</td></tr>
<tr><td colspan="7">Abbreviations: IV = intravenous; Q3W = every 3 weeks; QD = once daily.</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>2 arms</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact.

After a screening phase of up to 28 days, each participant will be assigned to receive study treatment until disease progression is radiographically documented and, when clinically appropriate, confirmed by the site per iRECIST; unacceptable AEs; intercurrent illness that prevents further administration of treatment; investigator’s decision to withdraw the participant; administrative reasons requiring cessation of treatment; or until the participant has received 35 administrations of pembrolizumab (approximately 2 years [24 months]). Vicriviroc will be discontinued when pembrolizumab is discontinued.

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

Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 and confirmed by the site per iRECIST, initiating a nonstudy cancer treatment, withdrawing consent, becoming lost to follow-up, or end of the study. All participants will be followed by telephone for OS until death, withdrawal of consent, becoming lost to follow-up, or the end of the study.</td></tr>
</table>

Study Governance Committees:

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

Regulatory, ethical, and study oversight considerations are outlined in Appendix 1

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The trial design is depicted in Figure 1.

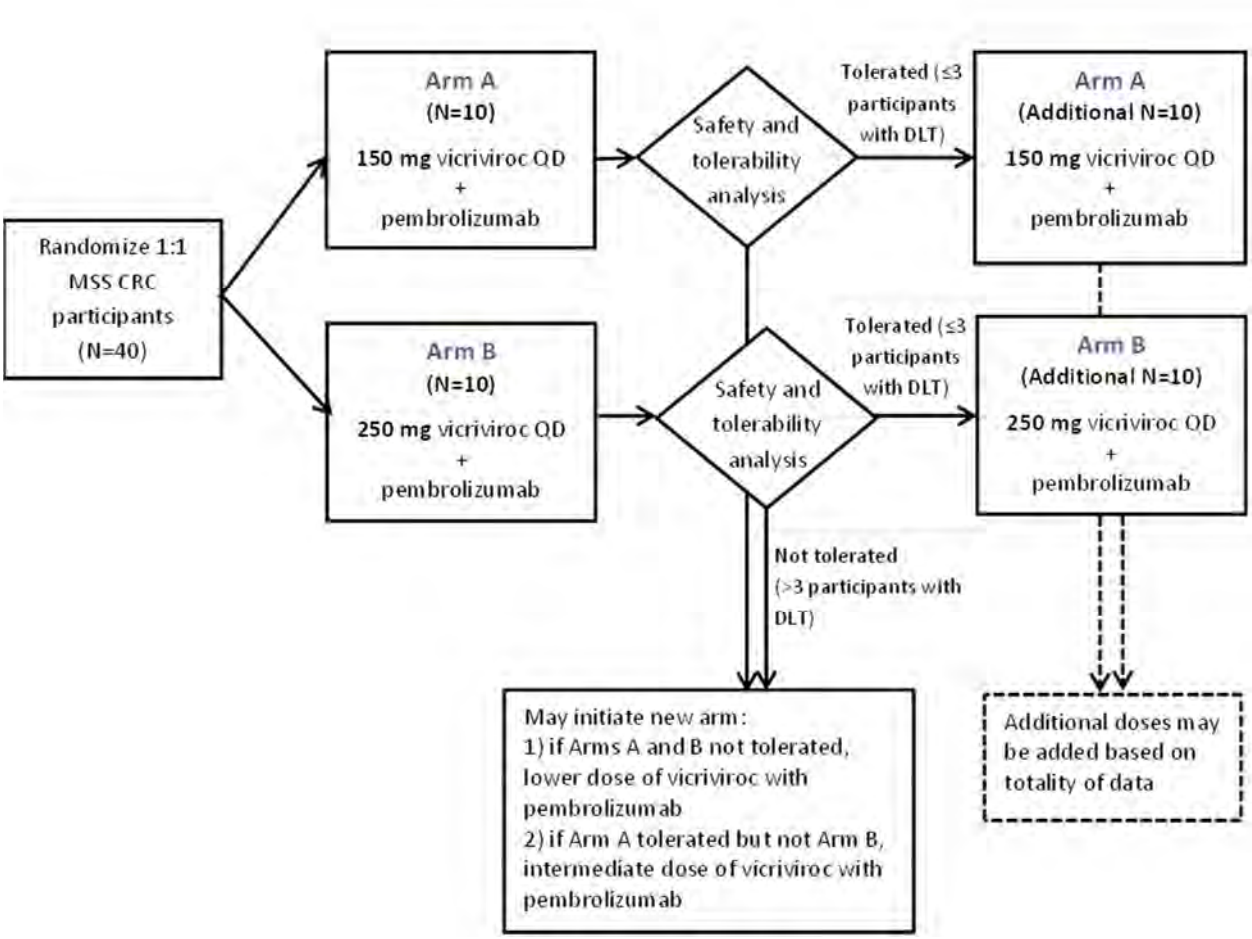

Figure 1 Trial Design

Abbreviations: CRC = colorectal cancer; DLT = dose-limiting toxicity; MSS = microsatellite stable; QD = once daily.

1.3 Schedule of Activities (SoA)

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Administrative Procedures													
Informed consent	X												
Reconsent at the first indication of radiographic progression		←										→	As assessed by the investigator.
Informed consent for future biomedical research	X												The participant may also provide consent for future biomedical research; however, the participant may participate in the main study without participating in future biomedical research.
Participant identification card	X												
Inclusion/exclusion criteria	X												
Demographic and medical history	X												
Oncology disease details and prior oncology treatment history	X												
Prior/concomitant medications review	X	←								→			

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Treatment randomization		X											Dose within 3 days of randomization.
Vicriviroc administration		←						→					• Arm A: 150 mg PO QD for 21 days per cycle or • Arm B: 250 mg PO QD for 21 days per cycle
Pembrolizumab administration		X		X		X		X					200 mg IV Q3W
Tumor imaging and response assessment	X*							X	X		X		*Screening imaging completed within 28 days before first dose. • On-treatment imaging every 9 weeks (±7 days) from first dose, or as clinically indicated, for the first year; and every 12 weeks thereafter. • Post-treatment imaging every 12 weeks (±14 days) from first dose, or as clinically indicated.

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Efficacy Procedures													
Subsequent antineoplastic therapy status									X	X	X	X	
Survival status		←						→				X	• After investigator determined PD or start of new anticancer treatment. • In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures/Assessments													**All screening procedures should be performed within 28 days of randomization, unless otherwise noted.**
Full physical examination	X								X	X			
Directed physical examination		X		X		X		X					
Height	X												
Weight	X	X		X		X		X	X	X			

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Vital signs	X	X		X		X		X	X	X			Heart rate, respiratory rate, blood pressure, temperature
12-lead ECG	X												Perform additional tests as clinically indicated.
ECOG performance status	X	X*		X		X		X	X	X			*Perform within 7 days of starting study intervention.
AE/SAE review	X	←								→	X*		*Collection during imaging follow-up would only be SAEs in the 90 days post-treatment discontinuation or until beginning another antineoplastic therapy.

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Laboratory Procedures/Assessments: Analysis by Local Laboratory													**All screening procedures should be performed within 28 days of randomization, unless otherwise noted.**
Serum β-HCG or urine pregnancy test (WOCBP only)	X												• Obtain urine pregnancy test within 72 hours before first dose. • Additional urine/serum testing may be performed if clinically warranted, and/or as defined by local regulations. • If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
Serum FSH (WOCBP only)	X												If necessary, to check menopausal status.
HIV, hepatitis B and C screen	X												Acceptable to be based on history, unless testing is required by local regulation.

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Urinalysis	X	X*		X		X		X					*If screening assessment has been performed within 72 hours before initiation of dosing, it does not need to be repeated on Cycle 1 Day 1. Otherwise, perform up to 72 hours before Day 1 dosing.
INR or PT and aPTT	X												Participants on anticoagulant therapy should be monitored throughout the trial as clinically indicated.
Comprehensive chemistry panel	X*	X		X		X		X	X	X			*If screening assessment has been performed within 72 hours before initiation of dosing, it does not need to be repeated on Cycle 1 Day 1. Otherwise, perform up to 72 hours before Day 1 dosing.

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
CBC with differential	X*	X		X		X		X	X	X			*If screening assessment has been performed within 72 hours before initiation of dosing, it does not need to be repeated on Cycle 1 Day 1. Otherwise, perform up to 72 hours before Day 1 dosing.
Thyroid function (T3 or FT3, T4 or FT4, and TSH)	X					X		X	X				To be performed every other cycle (3, 5, 7, etc.)
Liver function			X		X		X						
PK/PD/Future Biomedical Research/Biomarkers: Analysis by Central Laboratory													
Blood for genetic analysis		X											Collected predose from all randomized participants only. This is a requirement of the main study and is separate from the future biomedical research consent (as described in Sections 8.9 and 8.10).

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Blood for immune profiling (immunophenotyping)	X*	X*		X				X	X				*Collected at 2 distinct timepoints for Screening **AND** pre-dose C1D1. • Screening samples must be collected between -28 days to -3 days. • Collect predose samples 30 minutes before dosing on Day 1 of each cycle for Cycles 1, 2, and 4, and every 4 cycles thereafter.

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Serum for pembrolizumab PK*		X		X				X					*Predose (trough) PK samples will be collected within 24 hours before infusion at Cycles 1, 2, and 4, and every 4 cycles thereafter. • Cycle 1 Day 1: predose (0) and 0.5 h (within 30 minutes after end-of-infusion of MK-3475) • Cycle 2 Day 1: predose (0) and 0.5 h (within 30 minutes after end-of-infusion of MK-3475) • Cycle 4 Day 1: predose (trough) • After Cycle 4: predose every 4 cycles

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Plasma for vicriviroc PK*		X		X				X	X	X			*All predose vicriviroc PK samples must be collected within 10 min before dosing. • Cycle 1 Day 1: predose (0) and 1, 2, 4 (± 10 mins), and 8 h (± 30 mins) postdose • Cycle 2 Day 1: predose (0) and 1, 2, 4 (± 10 mins), and 8 h (± 30 mins) postdose • Cycle 4 Day 1: predose (trough) • After Cycle 4: predose every 4 cycles
Antipembrolizumab antibodies		X		X				X					Anti-pembrolizumab antibody samples will be collected within 24 hours before infusion at Cycles 1, 2, and 4 and every 4 cycles thereafter

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Blood for serum cytokines	X	X		X				X	X				• Screening samples must be collected between -28 days to -3 days. • Collect predose on Day 1 of each cycle for Cycles 1, 2, and 4, and every 4 cycles thereafter.
Blood for RNA analysis		X		X				X	X				Blood for RNA analyses should be collected predose on Day 1 of Cycle 1, Cycle 2, and Cycle 4 and at treatment discontinuation.

Trial Period	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**							**EOT/ Discont.**	**Post-treatment Phase**			**Notes**
Treatment Cycle	Screening (Visit 1)	1		2		3		4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Cycle Day (±3 days unless otherwise specified)	-28 to -1	1	11 (±4)	1	11 (±4)	1	11 (±4)	1	At time treatment discont. (+7)	30 days post last dose (+14)	Every 12 weeks (±14)	Every 12 weeks (±14)	Procedure windows may vary
Stool for biomarker analysis	X (2 samples)	X		X				X					Samples to be collected at home for all time points: • Collect first predose sample (optional) any time during screening between 7 and 4 days before Cycle 1 Day 1. • Collect second predose sample (required) at least 2 days after first predose sample. • Collect postdose samples (required) 2-5 days after dosing at Cycles 1, 2, 4, and 8, if clinically feasible.
Tumor Tissue Collection													
Archival and/or newly obtained tissue collection	X					X*							*Optional on-treatment biopsy (± 3 days). To be performed after scheduled blood draws.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; β-HCG = β human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous; PD = progressive disease; PK = pharmacokinetic(s); PO = per os (by mouth); PT = prothrombin time; QD = once daily; RNA = ribonucleic acid; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

2 INTRODUCTION

Vicriviroc maleate (also known as MK-7690, formerly SCH 417690 and SCH-D) is an orally available small molecule cysteine-cysteine motif chemokine receptor 5 (CCR5) antagonist. Once daily (QD) dosing of vicriviroc combined with pembrolizumab is currently being developed for the treatment of microsatellite stable (MSS) colorectal cancer (CRC).

2.1 Study Rationale

In both men and women, CRC is the third most commonly diagnosed type of cancer, and it is a leading cause of cancer-related deaths globally. The American Cancer Society estimates that approximately 4.6% of men (1 in 22) and 4.2% of women (1 in 24) will be diagnosed with colorectal cancer in their lifetime [American Cancer Society 2017]. The global burden of CRC is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 [Arnold, M., et al 2017]. The relative survival rate for CRC is 65% at 5 years following diagnosis and 58% at 10 years [American Cancer Society 2017].

CRC is a heterogeneous disease with a number of etiological pathways, including the chromosomal instability (CIN) pathway, the microsatellite instability (MSI) pathway, and CpG island methylator phenotype (CIMP). CRC may be divided via molecular phenotyping into tumors with normal deoxyribonucleic (DNA) mismatch repair (MMR) function and those with DNA MMR deficient (MMR-D). Tumors showing the presence of MSI are classified as MSI-H (microsatellite instability-high), depending on the extent of instability in the markers tested; whereas tumors without this characteristic are classified as MSS. MSI CRC composes approximately 15% of sporadic CRC and 5% of Stage IV CRC, while MSS CRC composes the remainder. Based on clinical data for pembrolizumab monotherapy, the immune-related objective response rate (ORR) was 0% (0 of 18 patients) for MMR proficient (MMR-P) CRC and 40% (4 of 10 patients) for MMR-D CRC [Le, D. T., et al 2015].

Metastatic colorectal cancer (mCRC) is characterized by an immunosuppressive environment created by suppressive cell types, such as myeloid-derived suppressor cells (MDSCs) and macrophages. Macrophages can either be tumor fighting (M1-subtype) or tumor helping (M2-subtype). In CRC, macrophages within the tumor (tumor-associated macrophages [TAMs]) are often of the tumor promoting M2-subtype. One of the master switches for determining whether a macrophage is tumor promoting (M2-subtype) versus tumor fighting (M1-subtype) is the CCR5 receptor. The G-protein–coupled receptor, CCR5, and its chemokine ligands (CCL3, CCL4, and CCL5) induce recruitment of stromal and inflammatory cells and promote immune evasion mechanisms. T cells at the invasive margins of human CRC liver metastases produce CCL5, which has tumor-promoting effects on tumor cells and TAMs (M2-subtype). In CRC explant models and human CRC tumor biopsies, CCR5 blockade led to repolarization of TAMs (M1-subtype), modulation of chemokines, a reduction of inflammatory cytokines (macrophage migration inhibitory factor [MIF], C-X-C motif ligand 8, interleukin-1 receptor antagonist, and vascular endothelial growth factor), an increase in interferon alfa (IFN-α) and interferon alfa-2a (IFN-α2a), and redistribution of infiltrating T cells. These alterations in the immune microenvironment could

potentially enhance the antitumor effects of antiprogrammed cell death 1 (anti-PD-1) treatment [Halama N, Zoernig I, Berthel A, Kahlert C, Klupp F, Suarez-Carmo 2016].

Moreover, CCR5-CCL5 signaling promotes the homing of immunosuppressive regulatory T cells (Tregs) in CRC and pancreatic cancer, and disruption of this signaling results in decreased migration of Tregs into the tumor and reduced tumor growth. In addition to its expression on immunosuppressive cell types such as Tregs, MDSCs, and TAMs, CCR5 and its ligands can also be expressed on T cells and NK (natural killer) cells. Studies are underway to better understand how inhibition of this axis balances the immune milieu to prevent cancer dissemination and to destroy tumor cells. CCR5 can also be expressed on tumor cells and in the stroma by cancer-associated fibroblasts. CCR5 is highly expressed by mCRC tumor cells, and CCR5 blockade can induce cytotoxic and apoptotic effects in CRC cancer cells [Weitzenfeld P, Ben-Baruch A 2014].

CCR5 antagonism has been shown to impact tumor progression and metastases in several tumor types (eg, gastric, breast, prostate) in nonclinical studies using xenograft models [Velasco-Velazquez, M., et al 2012] [Ochoa-Callejero, L., et al 2013] [Mencarelli, A., et al 2013]. In these models, the CCR5 antagonist maraviroc has been shown to reduce the potential for gastric and breast cancer cell dissemination, to prevent the development of gastric tumorigenesis, to reduce prostate cancer bone and brain metastases, and to impede recruitment of immunosuppressive TAMs in triple-negative breast cancer.

These data suggest that CCR5 antagonism might reverse tumor immune suppression caused by immune suppressive cell populations in the tumor microenvironment, such as MDSCs, Tregs, and TAMs. Reversal of this immunosuppression may allow immune checkpoint inhibitors (eg, PDL-1 antagonists) to be more effective against CRC, as well os other types of cancer. This proof-of-concept trial will investigate vicriviroc combined with pembrolizumab in advanced MSS CRC.

2.2 Background

Vicriviroc maleate is a potent CCR5 antagonist. Data for vicriviroc from human clinical trials for prior development in human immunodeficiency virus (HIV) indications demonstrated significant and substantial efficacy in reducing viral load and viral breakthrough by binding to CCR5 to block HIV entry. These data support on-target activity against CCR5. Safety data from these trials indicated vicriviroc was well tolerated in both healthy volunteers and patients with HIV. Development of vicriviroc was discontinued after pivotal studies failed to show improvement in HIV control with vicriviroc when added to optimized background therapy, compared with placebo.

Initial development of vicriviroc will focus on combinations with pembrolizumab. Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as

an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Refer to the Investigator's Brochures (IBs) and/or approved labeling for detailed background information on vicriviroc and pembrolizumab.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Inhibition of CCR5 as a Target for Cancer Treatment

Vicriviroc is a CCR5 antagonist that has previously been investigated in anti-HIV indications. There have been no previous clinical trials in oncology indications. For more details refer to the vicriviroc IB.

2.2.1.2 Inhibition of PD-1 as a Target for Cancer Treatment

Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications, refer to the pembrolizumab IB.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Vicriviroc Clinical Studies

Vicriviroc has been under development previously for HIV. More than 2100 participants have been exposed to vicriviroc in Phase 1 through Phase 3 studies, including 2 Phase 3 trials where a total of 568 participants were treated. The PK, pharmacodynamics, and safety of vicriviroc have been well characterized. Refer to the vicriviroc IB for further information.

2.2.2.2 Pembrolizumab Clinical Studies

Ongoing clinical trials with pembrolizumab are being conducted in multiple solid tumors. In addition, multiple combinations with pembrolizumab are also being investigated. Refer to the pembrolizumab IB for trial details.

2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

In participants with advanced/metastatic MSS CRC following administration of vicriviroc in combination with pembrolizumab by vicriviroc dosage treatment Arms A and B:

Objectives	Endpoints
Primary	
• Objective: To evaluate the objective response rate (ORR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).	• Objective response is a confirmed complete response (CR) or partial response (PR).
• Objective: To determine the safety and tolerability.	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuation of study treatment due to an AE
Secondary	
• Objective: To evaluate ORR as assessed by the investigator based on modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST) [Seymour, L., et al 2017], progression-free survival (PFS) as assessed by the investigator based on RECIST 1.1 and iRECIST, and overall survival (OS).	• Objective response is a confirmed CR or PR. • PFS is the time from the first dose of study intervention to the first documented disease progression or death due to any cause, whichever occurs first. • OS is the time from the first dose of study intervention to death due to any cause.
• Objective: To evaluate the pharmacokinetics (PK) of vicriviroc.	• PK parameters including AUC in nM·hr, maximum concentration (C_{max}) in nM, and trough concentration (C_{trough}) in nM
Tertiary/Exploratory	
• Objective: To evaluate the development of circulating antipembrolizumab antibodies.	• Antipembrolizumab antibody level
• Objective: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action.	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood ribonucleic acid (RNA) variation, proteomics and immunohistochemistry (IHC), and other biomarkers.

Objectives	Endpoints
• Objective: To determine if differential gut microbiome signatures are associated with response to treatment or development of adverse events.	• Gut microbiome composition, response, development of immune-related adverse events (irAEs), and changes in microbiome diversity.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, open-label, global, multisite Phase 2 trial of vicriviroc in combination with pembrolizumab in participants with MSS CRC. This trial will evaluate the safety, tolerability, and efficacy of vicriviroc in combination with pembrolizumab at 2 doses of vicriviroc: 150 mg (Arm A) and 250 mg (Arm B). The dose of pembrolizumab will remain constant at 200 mg every 3 weeks (Q3W). Lower and/or higher doses of vicriviroc may be explored depending on the combined safety, PK, and pharmacodynamic data available.

Participants will be randomly allocated to receive vicriviroc (150 mg or 250 mg) in combination with pembrolizumab using an interactive response technology (IRT). In Arms A and B, vicriviroc will be administered per os (PO) every day (QD) of a 21-day cycle; pembrolizumab will be administered IV Q3W on Day 1 of each cycle.

Initial enrollment in each dose arm will be staggered. The first 3 participants in Arm A or Arm B will be enrolled no more frequently than 1 participant per week, to allow for tolerability assessment between participants. Participants will be closely followed for unacceptable toxicities. After the first 10 evaluable participants in each arm have been enrolled, enrollment will be paused for safety and tolerability analysis until completion of the DLT period. If this arm is well tolerated (≤3 of 10 evaluable participants experience DLTs in Cycle 1), this arm may be expanded by enrolling an additional 10 participants. A dose arm will be considered intolerable if >3 of 10 evaluable participants experience DLTs in Cycle 1. If the dose arm is not tolerated, the arm may be discontinued, and the protocol may be amended to include a lower vicriviroc dose. Otherwise, enrollment into an arm will be discontinued, and alternative doses may be considered. Additional cohorts may be added based on the totality of the efficacy and safety data.

Participants will be monitored carefully for the development of AEs, and for clinical and/or radiographic evidence of disease progression according to RECIST 1.1. However, iRECIST may be used by the investigator for treatment decisions. In participants who have initial evidence of radiological progressive disease (PD) by RECIST 1.1, it will be at the discretion of the investigator whether to continue a participant on study intervention until repeat imaging is obtained. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may continue to receive study intervention until tumor assessment is repeated 4 to 8 weeks later to confirm PD by iRECIST per site assessment.

The investigator will evaluate AEs according to criteria outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, to establish the safety and tolerability of vicriviroc when administered in combination with pembrolizumab.

There will be no intraparticipant dose escalation for participants enrolled in this study. The definition of DLTs and criteria for dose modification of vicriviroc are outlined in Section 6.6.

Participants may receive study intervention for up to 35 cycles (24 months). Participants will be treated until PD, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the participant, participant completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study.

All participants will be followed for at least 30 days after their last dose of study drug therapy for AE monitoring. Serious adverse events (SAEs) will be collected for 90 days after discontinuation, 30 days if the participant initiates new anticancer therapy <30 days after discontinuation of study intervention, or the day new anticancer therapy is initiated if between 30 and 90 days after discontinuation of study intervention. Participants with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0 or 1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

Participants who discontinue treatment for reasons other than confirmed PD will have post-treatment follow-up for disease status (including imaging) until PD, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow-up.

After confirmed PD, each participant will be contacted by telephone every 12 weeks (84 days ± 14 days) for survival until withdrawal of consent, lost to follow up, death, or end of the study, whichever occurs first.

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

4.2 Scientific Rationale for Study Design

This Phase 2 trial is being conducted to evaluate the safety, efficacy, and tolerability of vicriviroc in advanced/metastatic MSS CRC when administered in combination with pembrolizumab. Vicriviroc has been previously developed for HIV indications and found to have a favorable toxicity profile (see Sec. 4.3.1 and the vicriviroc IB for more information). Vicriviroc has not been developed for oncology indications. Two different doses of vicriviroc (150 mg and 250 mg QD) will be evaluated in combination with the standard dose of pembrolizumab (200 mg Q3W).

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.2 Primary Efficacy Endpoint

A primary objective for this trial is to evaluate the antitumor activity of vicriviroc in combination with pembrolizumab in participants with MSS CRC. Tumor response in participants with solid tumors will be assessed using RECIST 1.1 based on investigator assessment.

This study will use ORR based on RECIST 1.1 criteria, as assessed the investigator, as the primary endpoint. The ORR is an acceptable measure of clinical benefit 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.

4.2.1.2.1 Secondary Efficacy Endpoints

Secondary objectives will include evaluation of PFS by RECIST 1.1 and ORR by iRECIST, and OS of participants treated with vicriviroc in combination with pembrolizumab. For additional details about assessing efficacy endpoints using RECIST 1.1 and iRECIST, see Appendix 8.

4.2.1.2.2 Response Rate Assessed by RECIST 1.1

RECIST 1.1 will be used to determine the objective response. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.2.3 Response Rate Assessed by iRECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen after treatment with pembrolizumab (Section 8.2.1.5). Immunotherapeutic agents such as vicriviroc and pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and participants treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had PD by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer OS than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into

account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

The iRECIST assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the United States Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. The investigators will use iRECIST to assess tumor response and progression and make treatment decisions.

4.2.1.3 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments will be safety endpoints in this study, including, but not limited to, the incidence of, causality, and outcome of DLTs, AEs, and discontinuation of study treatment due to AEs.

4.2.1.4 PK Endpoints

A secondary objective of this study is to characterize the PK profile of vicriviroc after administration of vicriviroc in combination with pembrolizumab. The systemic concentrations of this agent maybe used in conjunction with the pharmacodynamic, safety, and exploratory endpoint data to help assess future dosing strategies for vicriviroc.

PK endpoints will include AUC, C_{max}, and C_{trough}.

4.2.1.5 Antidrug Antibodies

Antidrug antibodies (ADA) response with pembrolizumab will be determined to understand drug metabolism, exposure, and safety. Formation of ADAs can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. ADA response at the beginning of each specified treatment cycle will be determined. The incidence of ADA and neutralizing ADA will be evaluated and summarized over time by dose. Correlations between the presence or absence of positivity for antidrug antibodies and PK and pharmacodynamic markers, activity, and safety may be explored.

4.2.1.6 Serum Cytokines

Because treatment with vicriviroc can result in immune stimulation and resulting potential for cytokine release, serum cytokines will be monitored to provide supplementary information to assist in the evaluation of any safety events (eg, tumor necrosis factor alpha [TNF-α] and interleukin 2 [IL-2] and 6 [IL-6]).

4.2.1.7 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. In addition to studying variation across the human genome, variants in CCR5 may specifically be investigated as there are variants in CCR5 known to impact function of the receptor. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies.

Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

Blood for immune profiling

Blood for immunophenotyping: Real-time biomarker analysis of immune markers on circulating immune cells will be performed to aid recommended phase two dose (RPTD) analysis.

Stool for biomarker analysis

Recent research suggests that the diversity of bacteria in the GI tract (microbiome) might be associated with response to checkpoint inhibition therapy and development of irAEs. In addition, the gut microbita influences the response to cancer immunotherapy and chemotherapy by affecting the differentiation and functions of myeloid cells in the tumor microenvironment. To evaluate the potential for such association in this study, stool will be collected and the diversity and strains of bacteria comprising the gut microbiome may be evaluated in the context of irAEs, clinical response to MK-7690, and changes to the diversity of the microbiome that result from the study treatment.

4.2.1.8 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research substudy are presented in Appendix 6.

4.3 Justification for Dose

4.3.1 Vicriviroc Dosing

Dose selection was based on available human clinical data. The 150-mg dose was selected because it provides equivalent AUC exposure to the Phase 3 dose of vicriviroc (30 mg PO QD boosted with ritonovir) used in the HIV trials. This exposure resulted in an approximately 3-log reduction in HIV RNA, and thus demonstrates significant viral activity. The higher dose of 250 mg, which may provide increased target coverage, was also shown to be well tolerated in previous human clinical trials.

The maximum preplanned dose of vicriviroc that will be used in this study is 250 mg QD. Higher doses may be considered if supported by clinical PK, pharmacodynamic, and efficacy data, although higher exposures are not likely to provide any substantial increase in target engagement. The study design allows for exploration of lower doses if the 150-mg dose level is not tolerated in combination with pembrolizumab.

The human starting dose and dosing interval of vicriviroc are based on an integration of nonclinical toxicologic, pharmacologic, and efficacy data. See the vicriviroc IB for more information.

4.3.2 Pembrolizumab Dosing

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications, regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W).

- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications.

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non–small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1-enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2, and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied, representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg dose (or 200-mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure–response relationships were also observed in other tumor types, including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose.

Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Male and/or female participants of at least 18 years of age with advanced/metastatic MSS CRC will be enrolled in this study.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Have a histologically proven locally advanced unresectable or metastatic (Stage IV) CRC.

2. Have locally confirmed MSS CRC. Participants with MSI-H/MMR-D or microsatellite unstable CRC are not eligible.

3. Have been previously treated with standard therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan, and have received, been intolerant to, or been ineligible for all treatment known to confer clinical benefit.

    a. Participants who have withdrawn from standard treatment because of unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will be eligible.

    b. Regimens given with adjuvant intent will be counted as treatment for metastatic disease if the participant's disease had progressed within 6 months after treatment.

4. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

5. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

    Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 7 days after the slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).

6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days of starting study intervention.

Demographics

7. Are Male or Female.

8. Are ≥18 years of age, inclusive, at the time of signing the ICF.

Male Participants

9. A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 120 days after the last dose of study intervention and refrain from donating sperm during this period.

Female Participants

10. A female participant is eligible to participate if she is not pregnant (Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:

    c. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

    OR

    d. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the last dose of study intervention.

Informed Consent

11. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial. The participant may also provide consent for future biomedical research; however, the participant may participate in the main study without participating in future biomedical research.

Laboratory Values

12. Have adequate organ function as defined by the following table (Table 1). Specimens must be collected within 28 days unless otherwise specified before the start of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin[a]	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine or Measured or calculated[b] CrCl (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	
INR or PT and aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR=glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; ULN = upper limit of normal.

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

[b] CrCl should be calculated per institutional standard.

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

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Have 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, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

2. Have known active central nervous system (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 that 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.

3. Have severe hypersensitivity reaction (≥Grade 3) to treatment with any mAb or components of the study interventions.

4. Have an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs), except vitiligo or resolved childhood asthma/atopy. Replacement therapy, such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, is not considered a form of systemic treatment and is allowed. Use of nonsystemic steroids is permitted.

5. Have a history of vasculitis.

6. Have an active infection requiring systemic therapy.

7. Have symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoracocentesis or paracentesis) is eligible.

8. Have interstitial lung disease that required oral or IV glucocorticoids to assist with management.

9. Have a history of pneumonitis (noninfectious) that required steroids, or has current pneumonitis.

10. Have a known history of HIV infection.

    Note: No HIV testing is required unless mandated by local health authority.

11. Have a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority.

12. Have a known history of active tuberculosis (TB; Bacillus tuberculosis).

13. Have 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, make administration of the study interventions hazardous, or make it difficult to monitor AEs, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

14. Have a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

15. Are pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study intervention.

16. Are WOCBP who have a positive urine pregnancy test within 72 hours before randomization or treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

    Note: In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative for the participant to start receiving the study intervention.

17. Have undergone major surgery and have not recovered adequately from any toxicity and/or complications from the intervention before starting study intervention.

18. Have a seizure disorder requiring ongoing antiseizure therapy or with any condition that, in the judgment of the investigator, is likely to increase the risk of seizure (eg, CNS malignancy or toxoplasmosis).

19. Have known GI disease or GI procedures that could interfere with the oral absorption or tolerance of vicriviroc, such as esophageal, gastric, or duodenal ulceration or inflammatory bowel disease, or history of GI surgery.

20. Are using any drug (therapeutic or recreational), or withdrawal thereof, that poses an increased risk of convulsions, in the opinion of the investigator.

21. Have had an allogeneic tissue/solid organ transplant.

Prior/Concomitant Therapy

22. Have received prior therapy with vicriviroc or other CCR5 antagonist (eg, maraviroc) or have received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent.

23. Have been treated with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX 40, CD137).

24. Have received prior systemic anticancer therapy, including investigational agents, or has used an investigational device within 28 days 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 or alopecia may be eligible. Participants receiving ongoing replacement hormone therapy for endocrine irAEs (eg, thyroid-replacement therapy) will not be excluded from participation in this study.

25. Have received prior radiotherapy (not to target lesions) 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.

26. Are expected to require any other form of antineoplastic therapy while on study.

27. Have a diagnosis of immunodeficiency, is receiving chronic systemic steroid therapy in excess of replacement doses (prednisone ≤10 mg/day is acceptable), or is taking any other form of immunosuppressive medication within 7 days before the first dose of the study intervention.

    Note: The use of physiologic replacement doses of corticosteroids may be approved after consultation with the Sponsor Medical Monitor or designee.

28. Have received a live-virus vaccine within 30 days before the first dose of the study intervention. Vaccines that do not contain live virus are permitted.

29. Are currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of cytochrome P450 (CYP)3A4 that cannot be discontinued for the duration of the study. The required washout period before starting study intervention is 2 weeks.

30. Are currently receiving either strong (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, St John's Wort) or moderate (eg, bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period before starting study intervention is 5 weeks for phenobarbital and 3 weeks for other agents.

Prior/Concurrent Clinical Study Experience

31. Are currently participating in or have participated in a study of an investigational agent, or have used an investigational device within 28 days 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.

5.3 Lifestyle Considerations

Participants should avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, and St. John's Wort (tablet or tea) while receiving study intervention. Otherwise, participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.1 Contraception

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

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

5.3.2 Pregnancy

If a participant inadvertently becomes pregnant while on study intervention, the participant will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates a female partner, the study personnel at the site must be informed immediately, and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.5.

5.3.3 Use in Nursing Women

It is unknown whether vicriviroc or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (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.

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 (study intervention(s) provided by the Sponsor) will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strengths	Dosage Levels	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Arm A	Experimental	Vicriviroc (MK-7690)	Drug	Tablet	30 mg	150 mg	Oral	QD	Experimental	IMP	Provided centrally by the Sponsor
Arm B	Experimental	Vicriviroc (MK-7690)	Drug	Tablet	50 mg	250 mg	Oral	QD	Experimental	IMP	Provided centrally by the Sponsor
Arm A and B	Experimental	Pembrolizumab (MK-3475)	Drug	Solution for infusion	100 mg/vial	200 mg	IV infusion	Q3W	Experimental	IMP	Provided centrally by the Sponsor
Abbreviations: IMP = investigational medicinal product; IV = intravenous; Q3W = every 3 weeks; QD = once daily.											

All supplies indicated in Table 2 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product per local guidelines unless otherwise instructed by the Sponsor.

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

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on the preparation and administration of pembrolizumab are provided in the Pharmacy Manual. There are no specific calculations or evaluations required to be performed to administer the proper dose of vicriviroc to each participant.

The rationale for selection of doses to be used in this study is provided in Section 4.3.

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

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to Arm A (150 mg vicriviroc QD plus pembrolizumab Q3W) or Arm B (250 mg vicriviroc QD plus pembrolizumab Q3W).

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol specified treatment plan for >3 weeks between vicriviroc or pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

Participants are prohibited from receiving the following concomitant therapies and vaccinations during the screening and treatment periods of the study:

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

- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion, provided that the participant has not progressed (either clinically or radiographically by iRECIST) or the lesion is not a target lesion, may be allowed at the investigator's discretion.

- Live vaccines within 30 days before the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest (ECI) that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

- CYP3A4 inhibitors/inducers/substrates are listed in Table 3. The participant must not take the treatments listed in Table 3 during the trial after the start of the study treatment. Since this list is not comprehensive, the investigator should use his or her medical judgment when a participant presents with a medication not on the list, or call the Sponsor Clinical Director for clarification.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

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 medication will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter products, herbal supplements, 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 before the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and ECIs, as defined in Section 8.4.7.

6.5.1 Inhibitors/Inducers of CYP3A4

Vicriviroc is a metabolism-dependent inhibitor of CYP3A4 and a substrate of CYP3A4. CYP3A4 inducers notably reduce vicriviroc exposure, while potent CYP3A4 inhibitors increase vicriviroc exposure. As such, concomitant use of other drugs that are identified in Table 3 as strong inducers, moderate inducers, strong inhibitors, or moderate inhibitors of CYP3A4 is prohibited while the participant is enrolled in this study.

Investigators should check an actively updated list of drugs that are clinically relevant inducers, or inhibitors of CYP450, including CYP3A4, as well as the product labeling of these compounds for reference (refer to Table 3 and Table 3 footnote c).

Table 3 Examples of CYP3A4 Inducers/Inhibitors Prohibited During the Trial

Strong 3A4 Inducers[a,e]	**Moderate 3A4 Inducers[b,e]**	**Strong CYP3A4 Inhibitors[c,e]**		**Moderate CYP3A4 Inhibitors[d,e]**
carbamazepine phenobarbital phenytoin rifabutin rifampin troglitazone	bosentan efavirenz etravirine modafinil	alprazolam atazanavir boceprevir cannabis (oral; IV) clarithromycin cobicistat conivaptan danoprevir and ritonavir dasabuvir diltiazem elvitegravir and ritonavir grapefruit juice[e] idelalisib indinavir and ritonavir itraconazole	ketoconazole lopinavir and ritonavir paritaprevir and ritonavir (ombitasvir and/or dasabuvir) posaconazole nefazodone nelfinavir ritonavir nefazodone saquinavir and ritonavir telaprevir telithromycin tipranavir and ritonavir troleandomycin voriconazole	amprenavir aprepitant cimetidine ciprofloxacin clotrimazole crizotinib cyclosporine dilitiazem dronedarone erythromycin fluconazole fluvoxamine fosamprenavir imatinib tofisopam verapamil grapefruit juice[f] star fruit juice

Abbreviations: AUC = area under the curve; CYP = cytochrome P450; IV = intravenous.

a Strong CYP3A4 inducers are those that decrease plasma AUC values of CYP3A4 substrates by >80% or higher.

b A moderate inducer decreases the AUC of a sensitive index CYP substrate by ≥50% to 80%.

c Strong inhibitors are defined as causing a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

d Moderate inhibitors are defined as causing a ≥2- but <5-fold increase in the AUC values or 50% to 80% decrease in clearance of sensitive CYP3A substrates when the inhibitors were given at the highest approved dose and the shortest dosing interval in clinical evaluations.

e Compiled from the table of substrates, inhibitors and inducers available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2 (“Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers”).

f The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).

6.5.2 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab and/or vicriviroc.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification

6.6.1 Dose Modification Guidelines

CTCAE, version 4.03, must be used to grade the severity of AEs. If appropriate, the investigator may attribute each toxicity event to vicriviroc or pembrolizumab alone, or to the combination and use the dose modification table (Table 4). If a dose modification for toxicity occurs with any agent, the dose may not be re-escalated in that participant. Dose modifications are always based on the previous cycle.

Participants may have 1 dose modification to vicriviroc and/or pembrolizumab throughout the course of the study (for modification of pembrolizumab, it may be held but the dose of 200 mg will not be changed). If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from study intervention. If a participant experiences several toxicities and there are conflicting recommendations, following the most conservative dose adjustment is recommended (dose reduction appropriate to the most severe toxicity).

If, in the opinion of the investigator, the toxicity is related to the combination of the 2 study interventions, both should be held according to recommended dose modifications in Table 4. If toxicity is strongly suspected to be due to 1 of the 2 study interventions, discuss with the Sponsor. For participant convenience, if 1 study intervention is delayed, then the second study intervention can be delayed until both can be administered.

AEs associated with vicriviroc and pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. According to existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation.

Vicriviroc and pembrolizumab will be held for Grade 4 hematologic toxicities, nonhematologic toxicities Grade 3 or higher including laboratory abnormalities, and severe or life-threatening AEs as per Table 4.

If toxicity does not resolve to Grade 0 or 1 within 12 weeks after the last dose of study intervention, study intervention should be discontinued after consultation with the Sponsor.

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

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

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Vicriviroc and/or Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where vicriviroc and/or pembrolizumab have been withheld, vicriviroc and/or pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg of prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.
4. If vicriviroc is withheld due to an AE (with or without withholding pembrolizumab) and is then restarted, it will be restarted at a lower dose. Participants at the 150-mg PO QD dose will be lowered to 90 mg PO QD; and participants at the 250-mg PO QD dose will be lowered to 150 mg PO QD. Only 1 dose reduction will be allowed. If further dose reduction is required, the participant should permanently discontinue vicriviroc.

irAEs	**Toxicity Grade or Conditions (NCI CTCAE v4.03)**	**Action Taken With Vicriviroc[a]**	**Action Taken With Pembrolizumab[b]**	**irAE Management With Corticosteroid and/or Other Therapies**	**Monitor and Follow up**
Pneumonitis	Grade 2	Withhold (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)	Withhold	– Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	– Monitor participants for signs and symptoms of pneumonitis. – Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. – Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue	Permanently discontinue		

irAEs	Toxicity Grade or Conditions (NCI CTCAE v4.03)	Action Taken With Vicriviroc[a]	Action Taken With Pembrolizumab[b]	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow up
Diarrhea/colitis	Grade 2 or 3	Withhold (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)	Withhold	– Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	– Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). – Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. – Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue	Permanently discontinue		
AST/ALT elevation or increased bilirubin	Grade 2	Withhold (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)	Withhold	– Administer corticosteroids (initial dose of 0.5-1 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 or 4	Permanently discontinue	Permanently discontinue	- Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	

irAEs	Toxicity Grade or Conditions (NCI CTCAE v4.03)	Action Taken With Vicriviroc[a]	Action Taken With Pembrolizumab[b]	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow up
T1DM or hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)	Withhold	- 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 (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)	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 (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)[b]	Withhold or permanently discontinue[b]		
Hyperthyroidism	Grade 2	Continue	Continue	- Treat with nonselective β-blockers (eg, propranolol) or thionamides as appropriate.	- Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)[b]	Withhold or permanently discontinue[b]		

irAEs	Toxicity Grade or Conditions (NCI CTCAE v4.03)	Action Taken With Vicriviroc[a]	Action Taken With Pembrolizumab[b]	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow up
Hypothyroidism	Grade 2-4	Continue	Continue	- Initiate thyroid-replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	- Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)	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	Permanently discontinue		

irAEs	Toxicity Grade or Conditions (NCI CTCAE v4.03)	Action Taken With Vicriviroc[a]	Action Taken With Pembrolizumab[b]	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow up
All other irAEs	Intolerable/ persistent Grade 2	Withhold (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)	Withhold	- Based on type and severity of AE administer corticosteroids.	- Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or permanently discontinue based on the type of event. Events that require discontinuation include and are not limited to Guillain-Barré syndrome, encephalitis (if pembrolizumab is restarted, restart vicriviroc at the lower dose level)[b]	Withhold or permanently discontinue based on the type of event. Events that require discontinuation include and are not limited to Guillain-Barré syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue	Permanently discontinue		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; irAE = immune-related adverse event; IV, intravenous; NCI = National Cancer Institute; PO = per os (by mouth); QD = daily; T1DM = type 1 diabetes mellitus.

[a] If pembrolizumab is withheld, vicriviroc will also be withheld.

[b] To withhold or permanently discontinue is at the discretion of the investigator or treating physician.

NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤Grade 2 and is controlled with hormone replacement therapy or achieved metabolic control (in case of T1DM).

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

Pembrolizumab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines for pembrolizumab-associated infusion reactions are provided in Table 5.

Table 5 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 hours	**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/hour to 50 mL/hour). 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 treatment with study intervention.**	Participant may be premedicated 1.5 hours (± 30 minutes) before infusion of pembrolizumab with: – Diphenhydramine, oral, 50 mg (or equivalent dose of antihistamine) – Acetaminophen, oral, 500-1000 mg (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include, but is not limited to: – Epinephrine** – IV fluids – Antihistamines – NSAIDs – Acetaminophen – Narcotics – Oxygen – Pressors – Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study intervention treatment.**	No subsequent dosing
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory. 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, version 4.03, at http://ctep.cancer.gov		

6.6.1.2 Other Allowed Dose Interruption for Pembrolizumab

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

6.6.2 Evaluation of Safety

To adequately evaluate the safety of the doses administered, all participants enrolled must meet the criteria for evaluability for Cycle 1.

Participants are considered nonevaluable for DLT evaluation if:

- They are randomized but not treated.
- They discontinue from the study before completing all the safety evaluations in Cycle 1 for reasons other than treatment-related AEs.
- They receive <75% of the total pembrolizumab infusion (eg, if the infusion had to be discontinued due to an infusion reaction) and/or vicriviroc in Cycle 1 and they did not experience a DLT.

6.6.2.1 Dose-limiting Toxicity

Formal DLT evaluation will be performed at the interim safety analysis, following completion of 1 cycle of treatment by 10 evaluable participants in each dose arm. DLT nonevaluable participants will not be replaced. For example, if 1 of the first 10 participants in an arm is nonevaluable for DLT, then the next DLT-evaluable participant enrolled and treated in the arm will be included in the interim safety analysis. The DLT evaluation period will be for 1 cycle (Day 1 to Day 21; Day 1 is considered the date a study intervention was first administered and not the date of randomization if dosing did not occur on the date of randomization). During this time, supportive treatment with granulocyte-colony stimulating factor (G-CSF) will not be allowed.

A dose arm will be considered intolerable if >3 of 10 evaluable participants experience DLTs in Cycle 1. If the dose arm is not tolerated, the arm may be discontinued, and the protocol may be amended to include a lower vicriviroc dose.

All toxicities will be graded based on investigator assessment (Appendix 3, Assessment of intensity).

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study treatment:

1. Grade 4 nonhematologic toxicity (not laboratory)

2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia

    a. Grade 4 thrombocytopenia of any duration

    b. Grade 3 thrombocytopenia associated with bleeding

3. Any nonhematologic AE Grade 3 severity (not laboratory) should be considered a DLT, with the following exceptions:
    - Grade 3 fatigue lasting ≤3 days;
    - Grade 3 diarrhea, nausea, or vomiting without use of antiemetics or antidiarrheals per standard of care;
    - Grade 3 rash without the use of corticosteroids or anti-inflammatory agents per standard of care.

4. Any Grade 3 or Grade 4 nonhematologic laboratory value (except clinically nonsignificant, treatable, or reversible laboratory abnormalities including uric acid) if:

    - Medical intervention is required to treat the participant, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >72 hours.

5. Any of the following liver test abnormalities are observed (Hy's Law):

    - ALT or AST >3 × ULN with total bilirubin >2 × ULN with no elevation in alkaline phosphatase (<2 × ULN)
    - No other reasons can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver diseases, or another drug capable of causing the observed injury

6. Febrile neutropenia Grade 3 or Grade 4:

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

7. Inability to administer ≥75% of the planned vicriviroc dose because of drug-related tolerability.

8. Delay in starting Cycle 2 by >2 weeks due to toxicity.

6.7 Intervention After the End of the Study

There is no study-specified intervention following 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.

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 prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts study treatment administration for more than 12 consecutive weeks, unless approved with written documentation from the Sponsor.
- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive urine or serum pregnancy test (see Section 10.5.3).

- Confirmed radiographic disease progression outlined in Section 8.11 (exception if the Sponsor approves treatment continuation).

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.

- Recurrent Grade 2 pneumonitis.

- Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination, including 2 doses of pembrolizumab and at least 80% of the planned doses of vicriviroc beyond the date when the initial CR was declared.

- Completion of 35 treatments (approximately 2 years) with vicriviroc and pembrolizumab.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study,as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

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

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

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

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

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (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 dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

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 written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

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

8.1.4 Medical History

8.1.4.1 General Medical History

A medical history will be obtained by the investigator or qualified designee.

Medical history will include all active conditions, drug allergies, significant medical procedures, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Any cancer, other than the cancer under study, will be recorded as medical history even if diagnosed greater than 10 years before enrollment. Details regarding the cancer under study will be recorded separately and not listed as medical history.

8.1.4.2 Oncologic Disease Details

The investigator or qualified designee will obtain historic and current details of the participant's cancer under study. This information will include, but is not limited to, date of diagnosis, stage, histology, locations of primary lesions, and location of metastases if applicable.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. Any medications taken to treat a cancer other than the cancer under study will be recorded as a prior medication even if taken greater than 28 days before the first dose of study medication. All treatments for the cancer under study will be recorded separately and not listed as a prior medication.

8.1.5.2 Prior Oncologic Treatment

The investigator or qualified designee will review and record all treatments for the cancer under study, including systemic and local treatment, vaccinations, radiation, and surgeries. Additional information collected on these treatments will include, but is not limited to, reason for discontinuation, best response, and date of progression after each treatment as applicable.

8.1.5.3 Concomitant Medications

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

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.3.

Any new anticancer therapy started after the participant's discontinuation from the treatment period will be recorded separately. Additional information collected on this treatment will include, but is not limited to, best response and date of progression.

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Vicriviroc

During on-site visits, daily morning administration of vicriviroc should be withheld and taken when witnessed by the investigator and/or trial staff. The administration, the dose, the time of administration, as well as any immediate reactions at the time of intake will be documented in the eCRF. The date and time of the last dose of vicriviroc (taken at home) should be documented in the eCRF.

For nonvisit days, vicriviroc will be taken at home.

When a participant attends a study visit, he or she will bring any unused tablets.

Refer to Section 8.1.8.1 (Timing of Dose Administration) for dose and treatment details.

Pembrolizumab

Administration of pembrolizumab will be witnessed by the investigator and/or study staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

Study treatment should begin within 3 days of randomization.

8.1.8.1 Timing of Dose Administration

Vicriviroc may be taken with or without food. Vicriviroc should be taken at approximately the same time each day.

On Day 1 of each 21-day cycle, after potential vicriviroc administration in the morning, pembrolizumab will be administered at a fixed dose of 200 mg as a 30-minute IV infusion.

8.1.9 Discontinuation and Withdrawal

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

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Domiciling

Participants will not be domiciled.

8.1.12 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days before the date of randomization. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of randomization.

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

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the date of first dose. Subsequent tumor imaging should be performed every 9 weeks (±7 days), or more frequently if clinically indicated, for the first year (through Week 54); and every 12 weeks thereafter. First post-treatment imaging assessment, after 105 weeks (735 days ±7 days), participants who remain on treatment will have imaging performed every 12 weeks (±14 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the central imaging vendor.

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

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 14-day window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging, using the same imaging schedule used while on treatment every 12 weeks (± 14 days) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response and date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.2.1.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging

should continue to be performed following the intervals as outlined in the SoA (Section 1.3) and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated as a flowchart in Figure 2.

Table 6 Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment, after patient reconsent, at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.
Abbreviations: iCPD = iRECIST-confirmed progressive disease; iCR = iRECIST complete response; iPR = iRECIST partial response; iRECIST = modified Response Evaluation Criteria in Solid Tumors version 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.				

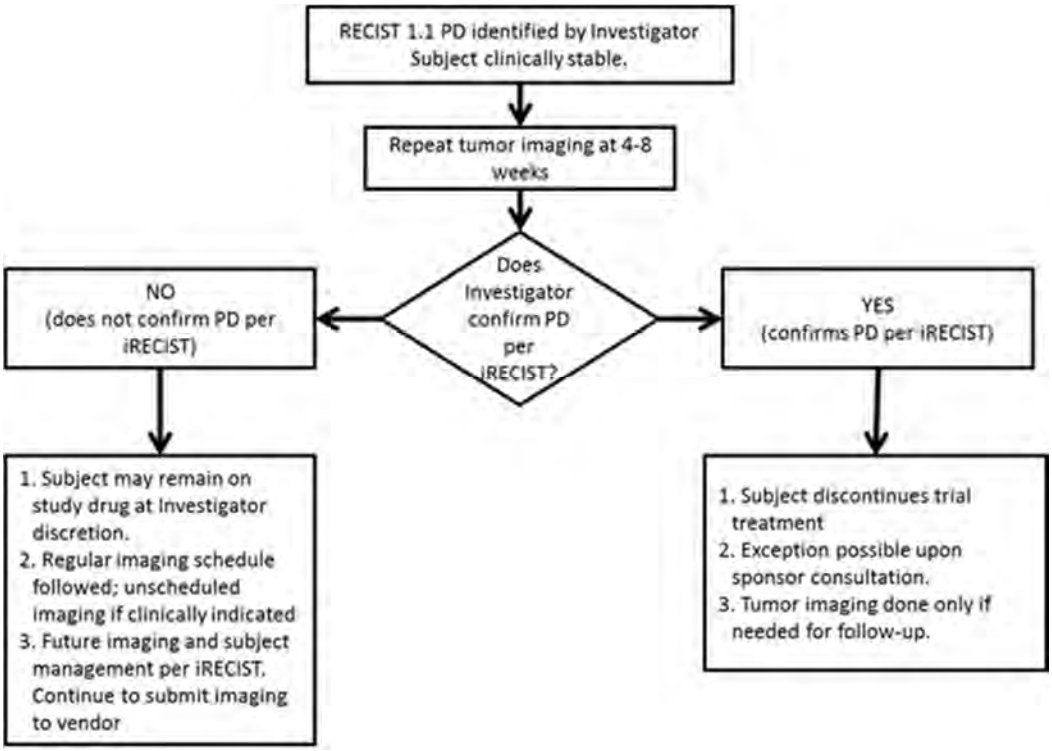

Figure 2 Imaging and Treatment for Clinically Stable Participants Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Investigator

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

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 Procedures Manual.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examination are described in the SoA (Section 1.3). After the first dose of trial treatment, 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 per the SoA (Section 1.3), the investigator or qualified designee will perform a directed physical examination as clinically indicated before trial treatment 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

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

8.3.3 Liver Function Tests

Liver function tests will be performed as specified in the SoA to check for potential liver toxicity in the combination therapy.

8.3.4 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the SoA (Section 1.3). Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

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 case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

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

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

Adverse events will not be collected for participants during the prescreening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy, etc., the participant is first required to provide consent to the main study, and AEs will be captured according to guidelines for standard AE reporting.

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

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

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

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

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

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

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

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

Type of Event	Reporting Time Period			Timeframe to Report Event and Follow-up Information to Sponsor
	Consent to Randomization	Randomization Through Protocol-specified Follow-up Period	After the Protocol-specified Follow-up Period	
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: - intervention related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/lactation exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requires regulatory reporting)	Report if: - due to intervention - causes exclusion	Report: - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (Does not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report: - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Abbreviations: ECI = event of clinical interest; DILI = drug-induced liver injury; NSAE = nonserious adverse 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 AE and/or SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

Efficacy endpoints as outlined in Section 8.2 will not be reported to the Sponsor, as described in Section 8.4.1.

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

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint 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 (ECIs)

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for vicriviroc of ≥600 mg/day (≥2 times the maximum indicated dose) or for pembrolizumab of ≥1000 mg (≥5 times the indicated dose). No specific information is available on the treatment of overdose of vicriviroc and pembrolizumab. In the event of overdose, vicriviroc and pembrolizumab should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of PK will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for PK

Sample collection, storage, and shipment instructions for serum samples will be provided in the Procedure Manual. PK samples should be drawn according to the PK collection schedule for all participants. Every effort should be taken to collect samples at 30 days after end of study treatment.

8.6.2 Blood Collection for Antipembrolizumab Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the Procedure Manual. Antipembrolizumab antibody samples should be drawn according to the ADA collection schedule for all participants (SoA). Every effort should be taken to collect samples at 30 days after end of study treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research
- Leftover RNA from blood for RNA analysis
- Leftover stool and/or its derivatives from stool for biomarker analysis
- Leftover main study tumor tissue

8.9 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for CCR5 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CCR5. Leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.10 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for genetic analysis
- Blood for immune profiling (immune-phenotyping)
- Blood for serum cytokines
- Blood for RNA analysis
- Stool for biomarker analysis
- Archival and/or newly obtained tissue collection

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the operations/laboratory manual].

8.11 Health Economics Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

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

8.12.1 Screening

Approximately 28 days before treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

Written consent must be obtained before performing any protocol-specific procedure. Results of a test performed before the participant signs the ICF 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 1 day before the first dose of study treatment except for the following:

- Laboratory tests are to be performed within 10 days before the first dose of study treatment. An exception is hepatitis testing, which may be done up to 28 days before the first dose of study treatment.

- Evaluation of ECOG is to be performed within 7 days *before* date of allocation/randomization.

- For WOCBP, a urine or serum pregnancy test will be performed within 72 hours before the first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Archival tumor sample collection is not required to be obtained within 28 days before the first dose of study treatment. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

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

8.12.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 9.1.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

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

8.12.4 Poststudy

8.12.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 (+14) days after the last dose of trial intervention or before the initiation of a new anticancer treatment, whichever comes first.

8.12.4.2 Imaging Follow-up

Participants who discontinue study treatment for a reason other than disease progression per RECIST 1.1/iRECIST will move into the Follow-Up Phase and should be assessed as outlined in the SoA (Section 1.3) to monitor disease status. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding

disease status until the start of new anticancer therapy, disease progression, death, or end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

8.12.4.3 Survival Follow-up

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

The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to an efficacy interim analysis, and/or final analysis. All participants who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

8.12.5 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested before, but not limited to, an 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 time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other nonconfirmatory analyses will be outlined in a separate supplemental statistical analysis plan (sSAP).

If, after the study has begun, changes are made to primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before final database lock, will be documented in the sSAP as needed and referenced in the clinical study report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full details are provided in the Statistical Analysis Plan (SAP), Section 9.2 through Section 9.12.

Study Design Overview	Phase 2 trial of vicriviroc in combination with pembrolizumab in participants with advanced/metastatic MSS CRC.
Analysis Populations	Efficacy (Primary and Secondary): Full Analysis Set (FAS) Safety (Primary): All Participants as Treated (APaT) and DLT evaluable population PK (Secondary): Per-Protocol (PP)
Primary Endpoint(s)	Efficacy: objective response is a confirmed CR or PR. Safety: DLT AE Discontinuing study treatment due to an AE
Secondary Endpoint(s)	Objective response is a confirmed CR or PR. PFS is the time from the first dose of study intervention to the first documented disease progression or death due to any cause, whichever occurs first. OS is the time from the first dose of study intervention to death due to any cause. PK parameters of vicriviroc in combination with pembrolizumab, including AUC in nM·hr, C_{max} in nM, and C_{trough} in nM·hr
Statistical Methods for Efficacy/ Pharmacokinetic Analyses	ORR will be estimated by treatment arm using an exact method based on the binomial distribution together with its 95% confidence interval (CI) (Clopper-Pearson interval). Methods for the secondary efficacy analyses will be documented in an sSAP. PK parameters of study interventions will be summarized by planned visit and time for each arm.
Treatment Assignment	Participants will be randomized centrally through IRT to the 2 arms (doses) of vicriviroc in combination with pembrolizumab.
Statistical Methods for Safety Analyses	Summary statistics will be provided by treatment arm for the safety endpoints as appropriate (eg, counts, percentages).

Interim Analyses	An interim safety analysis is planned for each arm after the first 10 evaluable participants have finished at least 1 cycle of therapy in a given arm. Additional interim safety analysis may be conducted to enable future trial planning at the Sponsor's discretion, and data will be examined on a continuous basis to allow for timely decisions.
Multiplicity	No multiplicity adjustment is planned in this Phase 2 trial.
Sample Size and Power	The total sample size is 20 participants per arm. No formal hypothesis testing will be conducted.

9.2 Responsibility for Analyses/In-house Blinding

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

The trial is open-label (ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned). Allocation to treatment will be randomized.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3 – Objectives/Hypotheses and Endpoints.

9.4 Analysis Endpoints

9.4.1 Efficacy/Pharmacokinetics Endpoints

ORR as assessed by the investigator based on RECIST 1.1 is the primary endpoint. ORR as assessed by the investigator based on iRECIST, PFS as assessed by the investigator based on RECIST 1.1 and iRECIST, and OS are the secondary endpoints in this study. A description of efficacy measures is provided in Section 8.2 – Efficacy Assessments.

ORR is defined as the proportion of participants who achieve a confirmed CR or PR.

PFS is defined as the time from the first dose of study intervention to the first documented disease progression or death due to any cause, whichever occurs first.

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

The PK endpoints include serum concentrations of vicriviroc, as well as derived PK parameters.

9.4.2 Safety Endpoints

The primary safety endpoint is the number and proportion of participants with DLTs, AEs, and discontinuation of study treatment due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 8.3 – Safety.

9.4.3 Exploratory Endpoints

Exploratory endpoints include:

- Antipembrolizumab antibody level
- Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood ribonucleic acid (RNA) variation, proteomics and IHC, and other biomarkers
- Gut microbiome composition, response, development of irAEs, and changes in microbiome diversity

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The FAS population will be used for the analyses of efficacy data in this study. It consists of all participants with a baseline scan that demonstrate measurable disease by the investigator's assessment and who are administered at least 1 dose of study intervention.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all participants who receive at least 1 dose of study intervention.

The DLT evaluable population includes APaT participants that meet the criteria for DLT evaluability (eg, finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 6.6.2.1 for details.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 Pharmacokinetic Analysis Populations

The PP population will be used for the analysis of PK data in this study. The PP population consists of the subset of participants who comply with the protocol sufficiently to ensure that their data will be likely to exhibit the effects of treatment, according to the underlying

scientific model. Compliance includes such considerations as exposure to treatment, availability of measurements, and the absence of major protocol violations. Any participants or data values excluded from the analyses will be identified, along with the reasons for exclusion, in the CSR. At the end of the study, all participants who were compliant with the study procedures and have available data from at least 1 treatment will be included in the PP analysis dataset.

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analysis

ORR will be estimated by treatment arm using an exact method based on the binomial distribution together with its 95% CI (Clopper-Pearson interval).

Methods for the secondary efficacy analyses will be documented in the sSAP.

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters, including DLTs, AEs, SAEs, laboratory tests, vital signs, and physical examinations.

DLT and AEs will be summarized by counts and frequencies for each arm. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate (eg, counts, percentages).

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

Demographic variables and baseline characteristics will be summarized.

9.6.3.2 Pharmacokinetic Analysis

The PK parameters of the study interventions will be summarized by planned visit and time for each arm separately.

9.7 Interim Analyses

An interim safety analysis is planned for each arm after the first 10 evaluable participants have finished at least 1 cycle of therapy in a given arm. If no more than 3 participants of the first 10 evaluable participants have experienced DLTs during the first cycle in a given arm, this arm may be expanded by enrolling an additional 10 participants. Otherwise, this arm may be terminated for safety concern.

Additional interim safety analysis may be conducted to enable future trial planning at the Sponsor's discretion, and data will be examined on a continuous basis to allow for timely decisions.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

The probability of observing more than 3 DLTs with 10 participants in each arm is shown in Table 8. When the true DLT incidence is 20%, there is a 12% chance to observe more than 3 DLTs with 10 participants in 1 arm.

The hypothetical ORR estimates and the CI (Clopper-Pearson interval [Clopper, C. J. 1934]) based on a sample size of 20 are shown in Table 9. Because of the small sample size, even an ORR as high as 20% (4 of 20) could be coming from a true signal as low as 7%. A higher ORR, such as 7 of 20, would be more indicative of a true response rate above 16%.

Table 8 Probability of Observing More Than 3 DLTs with 10 Participants in Each Arm

True DLT Incidence	Probability of Observing More Than 3 DLTs
10%	1.3%
15%	5.0%
20%	12.1%
25%	22.4%
30%	35.0%
Abbreviation: DLT = dose-limiting toxicity.	

Table 9 CI of the True ORR Under Different Hypothetical Number of Observed Response Scenarios With 20 Participants in Each Arm

Hypothetical Number of Responses (CR or PR)	ORR	95% CI of ORR
2	10%	(0.1%, 24.9%)
3	15%	(1.2%, 31.7%)
4	20%	(3.2%, 37.9%)
5	25%	(5.7%, 43.7%)
6	30%	(8.7%, 49.1%)
7	35%	(11.9%, 54.3%)
8	40%	(15.4%, 59.2%)
9	45%	(19.1%, 63.9%)
10	50%	(23.1%, 68.5%)

Abbreviations: CI = confidence interval; CR = complete response; ORR = objective response rate; PR = partial response.

9.10 Subgroup Analyses

Efficacy endpoints will be analyzed by arm. Additional subgroup analyses (eg, by age, gender, and race) may be conducted as needed and will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) 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 (eg, 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 (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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. Ethics Committee Review (Institutiona Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

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

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review 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 (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.6 Compliance with Law, Audit, and Debarmen

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); 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 Studies.

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

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

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

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

10.1.7 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 signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’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 may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.

Table 10 Protocol-required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit Hemoglobin	Albumin Alkaline phosphatase	Blood Glucose	Pregnancy test (serum or urine)[a]
Platelet count	ALT	Protein	PT/INR
WBC count with differential[d]:	AST	Specific gravity	aPTT or PTT
• Neutrophils	Bicarbonate	Microscopic examination, if abnormal results are noted	Total T3 (or FT3), total T4 (or FT4), and TSH[b,c]
• Lymphocytes	Calcium		
• Monocytes	Chloride		
• Eosinophils	Creatinine		
• Basophils	Glucose		
RBC count	Phosphorus		
RBC indices:	Potassium		
• MCV	Sodium		
• MCH	Total bilirubin		
• % Reticulocytes	Direct bilirubin		
	Total protein		
	Blood urea nitrogen		

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; FT3 = free triiodothyronine; FT4 = free thyroxine; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell; WOCBP = women of childbearing potential.

[a] Perform on WOCBP only 72 hours before Day 1 of Cycle 1. Pregnancy tests must be repeated before every cycle if required or as specified per local regulatory guidance.

[b] T3 is preferred; if not available, free T3 may be tested.

[c] If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Procedure Manual.

[d] Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, 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, or are considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

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

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- Is a new cancer (that is not a condition of the study)

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity

- 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 Common Terminology for Adverse Events (CTCAE), version 4.03. 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 activities of daily living (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 IRB/IEC.

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AE, SAE, 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 electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

This section is not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

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

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 hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).

- Male condom with cap, diaphragm, or sponge with spermicide.

- Male and female condom cannot be used together.

    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception, as described in Table 11, during the protocol-defined time frame in Section 5.1.

Table 11 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen-containing) hormonal contraception[b,c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen only hormonal contraception[b,c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant[b,c] ● Intrauterine hormone-releasing system[b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.
Notes: [a] Use 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 hormonal contraception efficacy is potentially decreased due to interaction with study intervention, condoms must be used in addition to the hormonal contraception during the intervention period and for at least 120 days after the last dose of study intervention. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those that inhibit ovulation.

10.5.3 Pregnancy Testing

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

Following initiation of treatment additional pregnancy testing will be performed if clinically warranted, and/or as defined by local regulations.

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

- 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.

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.

- **Scope of Future Biomedical Research**

The specimens consented and/or collected in this study as outlined in Section 8.10 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 drugs/vaccines may interact with
- 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.

- **Summary of Procedures for Future Biomedical Research**.

1. Participants for Enrollment

   All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

2. 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.

3. 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.

4. 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.

- **Confidential Participant Information for Future Biomedical Research**

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' 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 gender, age, medical history and treatment outcomes are 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 which 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.

- **Biorepository Specimen Usage**

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing 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 this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

- **Withdrawal From Future Biomedical Research**

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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.

- **Retention of Specimens**

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main 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 utilized 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.

- **Data Security**

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.

- **Reporting of Future Biomedical Research Data to Participants**

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.

- **Future Biomedical Research Study Population**

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

- **Risks Versus Benefits of Future Biomedical Research**

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.

- **Questions**

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

- **References**

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10.7 Appendix 7: Country-specific Requirements

This section is not applicable.

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

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

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

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

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

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

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

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

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Nontarget.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new nontarget lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is “reset”. This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the SoA (Section 1.3).

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

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

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
β-HCG	β human chorionic gonadotropin
BCG	Bacillus Calmette-Guérin
CCR5	cysteine-cysteine motif chemokine receptor 5
CI	confidence interval
CIMP	CpG island methylator phenotype
CIN	chromosomal instability
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram

Abbreviation	Expanded Term
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EOT	end of treatment
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization
iCPD	confirmed radiographic progression
IEC	Independent Ethics Committee
IFN-α	interferon alfa
IFN-α2a	interferon alfa-2a
IHC	immunohistochemistry
IL-2	interleukin 2
IL-6	interleukin 6
INR	international normalized ratio
irAEs	immune-related adverse events

Abbreviation	Expanded Term
IRB	Institutional Review Board
iRECIST	modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
IV	intravenous
mAb	monoclonal antibody
mCRC	metastatic colorectal cancer
MDSC	myeloid-derived suppressor cell
MMR	mismatch repair
MMR-D	mismatch repair deficient
MMR-P	mismatch repair proficient
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
NCI	National Cancer Institute
NK	natural killer (cells)
NSAID	nonsteroidal anti-inflammatory
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBPK	physiologically based PK
PD	progressive disease
PD-1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os (by mouth)
PP	Per-protocol
PR	partial response
PT	prothrombin time

Abbreviation	Expanded Term
Q2W	every 2 weeks
Q3W	every 3 weeks
QD	once daily
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental statistical analysis plan
T3	triiodothyronine
T4	thyroxine
TAM	tumor-associated macrophage
TB	tuberculosis
TNF-α	tumor necrosis factor alpha
Tregs	regulatory T cells
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WOCBP	woman/women of childbearing potential

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