Official Protocol Title:	A Phase II Study of Navarixin (MK-7123) in Combination with Pembrolizumab (MK-3475) in Participants with Selected Advanced/Metastatic Solid Tumors
NCT number:	NCT03473925
Document Date:	22-March-2018

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Phase II Study of Navarixin (MK-7123) in Combination with Pembrolizumab (MK-3475) in Participants with Selected Advanced/Metastatic Solid Tumors

Protocol Number: 034-01

Compound Number: MK-7123

Sponsor Name and Legal Registered Address:

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

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND NUMBER: 137,203

EudraCT NUMBER: Not Applicable

Approval Date: 22-Mar-2018

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 01

Overall Rationale for the Amendment:

Revisions/updates incorporated based on feedback from regulatory agency, data management, and sites.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities (SoA)	Addition of row in Efficacy Procedures section for MSI testing of tumor sample in participants with CRPC who show a response to treatment	To assist in interpreting response to treatment in the CRPC participant population.
9.2.3 MSI Status	Information noting that MSI testing will be performed on tumor samples from CRPC participants who show a response to treatment	To align with the change made to the Schedule of Activities described in the row above. (To assist in interpreting response to treatment in the CRPC participant population)
2. Schedule of Activities (SoA)	In Notes cell of Hematology row: Revision of description of time points for collection of hematology (including ANC) blood samples.	This change is made to remove ambiguity regarding collection of ANC samples: • As a safety lab, hematology (including ANC) will be collected on Day 1 of every cycle pre-dose as follows: ▪ On days when navarixin PK samples are collected, pre-dose ANC should be collected within 2 hours prior to dosing. ▪ On days when navarixin PK is not collected, pre-dose ANC can be collected within 24 hours prior to dosing • An additional sample (for pharmacodynamics assessment) will be collected between 6-12 hours after dosing on Days 1, 3, and 8 of Cycle 1, and Day 1 of Cycle 2.

Section # and Name	Description of Change	Brief Rationale
9.7 Pharmacodynamics	Removal of the phrase "After Cycle 4: Same scheme as Pembro PK" from description of when venous samples for ANC are to be collected.	To align with the change made to the Schedule of Activities described in the row above. (To remove ambiguity regarding collection of ANC samples)
2. Schedule of Activities (SoA)	In Notes cell of Comprehensive Chemistry Panel row: Revision of description of time points for collection of chemistry panel blood samples.	The following change is made to allow chemistry samples to be collected at the same time as hematology samples: • Chemistry panel will be collected on Day 1 of every cycle pre-dose as follows: ▪ On days when navarixin PK samples are collected, pre-dose sample should be collected within 2 hours prior to dosing. ▪ On days when navarixin PK is **not** collected, pre-dose sample can be collected within 24 hours prior to dosing.
2. Schedule of Activities (SoA)	In Notes cell of Thyroid Function (T3, or FT3, T4 or FT4, and TSH) Testing row: Revision of description of time points for collection of thyroid testing blood samples.	The following change is made to allow thyroid function samples to be collected at the same time as hematology samples: • Thyroid testing will be collected on Day 1 of every cycle pre-dose as follows: ▪ On days when navarixin PK samples are collected, pre-dose sample should be collected within 2 hours prior to dosing. ▪ On days when navarixin PK is **not** collected, pre-dose sample can be collected within 24 hours prior to dosing.

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design	Added clarifying language regarding discontinuing enrollment in an arm due to DLTs in Stage 1.	The following sentence is added to ensure participant safety: However, during Stage 1, **if at any time >3 DLTs are observed within the first 10 evaluable participants**, enrollment into an arm will be discontinued.
5.1 Overall Design	Stopping rule for excessive toxicity occurring outside the protocol defined window is added.	This change is made to ensure participant safety.
5.1.3 Dose Limiting Toxicity	Definition of DLT is modified.	The following criteria for anemia are added to expand the definition of DLT: • Grade 4 anemia of any duration • Grade 3 anemia lasting >7 days or requiring transfusion
6.1 Exclusion Criteria	Exclusion Criterion #4 is modified, adding the sentence "In addition to active autoimmune disease, participants who have previously been permanently discontinued from PD-(L)1 therapy due to immune related side effects are not eligible for the study."	This change is made for participant safety.
6.1 Exclusion Criteria	Exclusion criterion #5, "History of vasculitis" is deleted. (list of criteria has been renumbered)	Vasculitis is not a risk for navarixin or pembrolizumab.

Section # and Name	Description of Change	Brief Rationale
6.1 Exclusion Criteria	Exclusion criterion #12 (previously criterion #13) is modified to include history or evidence of gastrointestinal condition(s) or impaired liver function or diseases that may significantly alter absorption or metabolism of oral medication.	This change is made because navarixin is administered orally.
9.1.12 Calibration of Equipment	Bulleted list of critical equipment for the trial is deleted.	This change is made per process update.
9.2.1.3 End of Treatment and Follow-up Tumor Imaging	Monitoring disease status by tumor imaging is changed from every 9 weeks to every 12 weeks (±7 days).	This change corrects the end of treatment and follow-up tumor imaging interval to be consistent with that shown in the Schedule of Activities.
9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information	The time period and frequency for collection of AE, SAE and other reportable safety event information is corrected.	This correction ensures alignment of the time period and frequency of data collection with pembrolizumab protocol standards and is consistent with other sections of the protocol.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. Synopsis

Protocol Title:

A Phase II Study of Navarixin (MK-7123) in Combination with Pembrolizumab (MK-3475) in Participants with Selected Advanced/Metastatic Solid Tumors

Short Title:

A Phase II Study of Navarixin (MK-7123) in Combination with Pembrolizumab (MK-3475) in Participants with Selected Advanced/Metastatic Solid Tumors

Objectives/Hypotheses and Endpoints:

Male/female participants of at least 18 years of age with selected advanced/metastatic solid tumors will be enrolled in this study.

Objective	Endpoint
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) following administration of navarixin in combination with pembrolizumab.	• Objective response is a confirmed complete response (CR) or partial response (PR).
• Objective: To determine the safety and tolerability of navarixin in combination with pembrolizumab.	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study treatment due to an AE.
Secondary	
• Objective: To evaluate objective response rate (ORR) as assessed by investigator based on iRecist (modified RECIST 1.1), progression-free survival (PFS) as assessed by RECIST and iRECIST and overall survival (OS) following administration of navarixin in combination with pembrolizumab.	• Objective response is a confirmed CR or PR. • PFS is time from the first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first. • OS is time from the first dose of study medication to death due to any cause.
• Objective: To evaluate the pharmacodynamics as measured by absolute neutrophil counts (ANC) following administration of navarixin in combination with pembrolizumab.	• ANC in 10^9/L

• Objective: To evaluate the pharmacokinetics of navarixin when administered in combination with pembrolizumab.	• Pharmacokinetic parameters including area under the curve (AUC) in ng·hr/mL, maximum concentration (C_{max}) in ng/mL, trough concentration (C_{trough}) in ng/mL

Overall Design:

Study Phase	Phase 2
Clinical Indication	Treatment of participants with advanced/metastatic solid tumors.
Population	Participants with histologically or cytologically confirmed advanced/metastatic solid tumors in 3 selected tumor types.
Study Type	Interventional
Type of Design	This is a stratified, parallel, 2-dose randomized (1:1), uncontrolled multicenter study of navarixin in combination with pembrolizumab. The study will use a 2-stage adaptive design based on pre-specified criteria for response rate.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 120 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Participants will be stratified by tumor type and randomized 1:1 to either of 2 dose level arms: Arm A will receive 30 mg navarixin orally QD + pembrolizumab 200 mg IV Q3W; Arm B will receive 100 mg navarixin orally QD + pembrolizumab 200 mg IV Q3W. In Stage 1 of the study, 30 participants will be randomized to each arm. In Stage 2, barring early termination of the arm, 30 additional participants will be randomized to each arm.
Duration of Participation	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 modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the participant, noncompliance with study treatment or procedure requirements, administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations (approximately 2 years) of combination treatment with navarixin and pembrolizumab. Monotherapy treatment with pembrolizumab will be allowed if navarixin treatment is withheld for ANC or febrile neutropenia. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3. 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, when clinically appropriate, confirmed by the site per iRECIST, initiating a non-study cancer treatment, withdrawing consent, becoming lost to follow-up or the end of the study. All participants will be followed by telephone for overall survival until death, participant withdrawal of consent, becoming lost to follow-up or the end of the study.

Study governance considerations are outlined in Appendix 1. A list of abbreviations used in this document can be found in Appendix 6.

2. Schedule of Activities (SoA)

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
Administrative Procedures												
Informed Consent	X											
Informed Consent for Future Biomedical Research	X											
Participant Identification Card	X											
Inclusion/Exclusion Criteria	X											
Demographic and Medical History	X											
Oncology Disease Details and Prior Oncology Treatment History	X											
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X			
Treatment Randomization		X										Dose within 3 days of randomization

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
Navarixin Administration		←					→					Navarixin doses: Arm A: 30 mg orally QD or Arm B: 100 mg orally QD
Pembrolizumab Administration		X			X	X	X					Pembrolizumab dose: 200 mg IV Q3W
Efficacy Procedures												
Tumor Imaging and Response Assessment	X						X	X		X		Screening imaging within 28 days of first dose. On-study imaging every 9 weeks (±7 days) from first dose, or as clinically indicated
MSI status testing of tumor tissue from CRPC participants	X*											*CRPC participants who have an objective response (confirmed or unconfirmed) to therapy will complete, if not previously done on an archival or newly obtained tumor sample. Testing need only be completed once.
Subsequent anti-neoplastic therapy status								X	X	X	X	

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
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												
Full physical examination	X							X	X			
Directed Physical Examination		X			X	X	X					
Height	X											
Weight	X	X			X	X	X	X	X			
Vital Signs	X	X			X	X	X	X	X			VS: heart rate, respiratory rate, blood pressure, temperature
12-lead ECG	X											Perform additional test as clinically indicated.
ECOG Performance Status	X	X			X	X	X	X	X			

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
Laboratory Procedures/Assessments – Analysis by Local Lab												
Serum β-Human Chorionic Gonadotropin or Urine Pregnancy Test (β-hCG; Women of childbearing potential (WOCBP) only)	X											• 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. • Obtain urine pregnancy test within 72 hours prior to first dose.
Serum Follicle Stimulating Hormone (FSH) - (WOCBP only)	X											If necessary, to check menopausal status
HIV, Hepatitis B and C Screen (per site SOP)]	X											Acceptable to be based on history unless testing is required by local regulation.
Urinalysis	X*	X			X	X	X					*If screening assessment has been performed within 72 hours prior to initiation of dosing, it does not need to be repeated on Cycle 1 Day 1. Perform up to 72 hours before Day 1 dosing;

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
Hematology including ***absolute neutrophil count (ANC)***	X	X	X	X	X	X	X	X	X			**Note: visit windows for this assessment vary as follows:** • As a safety lab, hematology (including ANC) will be collected on Day 1 of every cycle pre-dose as follows: ▪ On days when navarixin PK samples are collected, pre-dose ANC should be collected within 2 hours prior to dosing. ▪ On days when navarixin PK is **not** collected, pre-dose ANC can be collected within 24 hours prior to dosing. • In addition, for pharmacodynamics assessment, another sample will be collected between 6-12 hours after dosing on Days 1, 3, and 8 of Cycle 1, and Day 1 of Cycle 2.
PT/INR and aPTT	X											Participants on anticoagulant therapy should be monitored throughout the trial.

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
Comprehensive Chemistry Panel	X	X			X	X	X	X	X			**Note: visit windows for this assessment vary as follows (to be collected at same time as hematology samples):** • Chemistry panel will be collected on Day 1 of every cycle pre-dose as follows: ▪ On days when navarixin PK samples are collected, pre-dose sample should be collected within 2 hours prior to dosing. ▪ On days when navarixin PK is **not** collected, pre-dose sample can be collected within 24 hours prior to dosing.

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
Thyroid Function (T3, or FT3, T4 or FT4, and TSH)		X				X	X	X				**To be performed every other cycle (1, 3, 5, 7 etc.)** **Note: visit windows for this assessment vary as follows (to be collected at same time as hematology samples):** • Thyroid testing will be collected on Day 1 of every cycle pre-dose as follows: ▪ On days when navarixin PK samples are collected, pre-dose sample should be collected within 2 hours prior to dosing. ▪ On days when navarixin PK is **not** collected, pre-dose sample can be collected within 24 hours prior to dosing
Prostate-Specific Antigen (PSA)	X						X			X		Screening PSA within 28 days of date of allocation. In the first year, on-study PSA every 9 weeks (±7 days) from date of allocation. After 1 year, in participants remaining on-study, PSA every 12 weeks (±7 days)

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
AE/SAE review	X	←						→		X		
Pharmacokinetics/Pharmacodynamics/Future Biomedical Research/Biomarkers – Analysis by Central Lab												
Blood for Genetic Analysis		X										Collect pre-dose.
Peripheral Blood Mononuclear Cell		X			X	X	X	X				Collect pre-dose (up to 24 hours before dosing) on Day 1 of Cycles 1-4, 6, and 8, and every 4 Cycles thereafter.
Blood for Immune Profiling (immunophenotyping)		X			X	X	X	X				Collect pre-dose (up to 24 hours before dosing) on Day 1 of each Cycle for Cycles 1-4, 6 and 8, and every 4 Cycles thereafter.
Serum for Pembrolizumab Pharmacokinetics		X			X		X					Pre-dose (trough) PK samples will be collected within 24 hours before infusion at Cycles 1, 2, 4, 6, and 8 and every 4 cycles thereafter

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
Plasma for navarixin Pharmacokinetics		X	X	X	X	X	X	X	X			**Note:** All pre-dose navarixin PK samples must be collected within 10 minutes prior to dosing. **Cycle 1:** **Day 1:** Pre-dose (0), 1, 2, 4, and 6 h, and 1 sample between 8 -12 h **Day 3:** Pre-dose, 1 sample between 6 – 12 h **Day 8:** Pre-dose, 1 sample between 6 - 12 h **Cycle 2:** **Day 1:** Pre-dose (0), 1, 2, 4, and 6 h, and 1 sample between 8 -12 h **Cycle 3:** **Day 1:** Pre-dose (trough) **Cycle 4:** **Day 1:** Pre-dose (trough) **After Cycle 4:** Same scheme as for pembrolizumab PK

Trial Period:	**Screening Phase**	**Treatment Phase (21-day Treatment Cycles)**						**End of Treatment (EOT) / Discon-tinuation**	**Post-Treatment Phase**			**Notes**
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**			**2**	**3**	**4 to 35**		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		**1**	**3**	**8**	**1**	**1**	**1**	**At time of treatment discon.**	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Visit Window (Days)	**-28 to -1**				**± 3**	**± 3**	**± 3**	**+7**	**+7**	**± 7**	**± 7**	Procedure windows may vary
Anti-Pembrolizumab Antibodies		X			X		X					Anti-pembrolizumab antibody samples will be collected within 24 hours before infusion at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter
Blood for Serum Protein Analysis		X			X	X	X					Blood for serum protein analysis should be collected pre-dose on Day 1 of each Cycle.
Blood for RNA Analysis		X			X		X	X				Blood for RNA Analyses should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 5, and at treatment discontinuation
Tumor Tissue Collection												
Archival and/or Newly Obtained Tissue Collection	X					X*						*optional on-treatment biopsy. To be performed after scheduled blood draws.

3. Introduction

Navarixin (MK-7123, formerly SCH 527123), is an orally bioavailable, potent, and specific small molecule antagonist of the CXC G protein-coupled receptor CXCR1/2, with substantially higher affinity for CXCR2 than CXCR1. It is in development for once daily dosing for use in combination therapy with pembrolizumab for the treatment of advanced solid tumors. Three tumor types will be evaluated in this study: PD-(L)1 refractory non-small cell lung cancer (NSCLC), castration resistant prostate cancer, and microsatellite stable (MSS) colorectal cancer (CRC).

3.1 Study Rationale

Myeloid-derived suppressor cells (MDSCs) are an adverse cancer-wide prognostic population of immune infiltrating cells [Gentles, A. J., et al 2015]. MDSCs contribute to tumor immune evasion through a variety of mechanisms that suppress local T-cell activation and viability [Gentles, A. J., et al 2015] [Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. 2015]. MDSCs can also influence tumor progression by promoting tumor metastases, angiogenesis and tumor cell invasion [Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. 2015]. The relief of myeloid suppression of T cell function could enhance pembrolizumab responses and this mechanism is being actively interrogated to increase the number of durable clinical responses.

The CXC G protein-coupled receptor, CXCR2, is highly expressed on human MDSCs and plays a role in the homing of MDSCs in the tumor microenvironment (TME). The CXCR2 receptor is highly expressed across tumor types and has been shown to significantly correlate with poor survival [Steele CW, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R 2016] [Saintigny, P., et al 2013] [Li, L., et al 2015]; internal Moffitt/TCGA database analysis).

For example, in late stage prostate cancer, CXCR2-MDSCs have been suggested to play a critical role in prostate tumor progression [Wang G, Lu X, Dey P, Deng P, Wu CC, Jiang S 2016]. Hormonal therapy and chemotherapy have been shown to enrich for CXCR2 positive cells in prostate cancer patients. In addition to promoting tumor resistance by enhancing the immunosuppressive TME through MDSC recruitment, reports have shown that the ELRCXC chemokine-CXCR1/2 axis can promote angiogenic responses and activate epithelial-mesenchymal transition (EMT) differentiation programs which are associated with its role in metastasis and stemness [David JM, Dominguez C, Hamilton DH, Palena C. 2016] [Acharyya S, Oskarsson T, Vanharanta S, Malladi S, Kim J 2012].

This Phase 2 POC trial will investigate 3 tumor types that express CXCR2, and have a low objective response rate to PD-(L)1 inhibitor monotherapy: NSCLC (PD-(L)1 refractory), castration resistant prostate, and MSS colorectal cancers, in order to test the hypothesis that navarixin added to pembrolizumab may improve treatment outcomes.

3.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on navarixin and the MK-3475 IB/approved labeling for detailed background information on pembrolizumab.

3.2.1 Pharmaceutical and Therapeutic Background

Navarixin is a CXCR2 antagonist.

3.2.1.1 Navarixin Pharmaceutical and Therapeutic Background

The ELRCXC chemokine-CXCR1/2 axis mediates pleiotropic effects that impact tumorigenesis: 1) promotion of tumor resistance by enhancing the immunosuppressive tumor microenvironment (TME) by recruitment of neutrophils/myeloid-derived suppressor cells (MDSCs), 2) promotion of angiogenic responses, and 3) activation of epithelial-mesenchyme transition (EMT), which is associated with metastasis and stemness [David JM, Dominguez C, Hamilton DH, Palena C. 2016] [Acharyya S, Oskarsson T, Vanharanta S, Malladi S, Kim J 2012] [Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. 2015].

CXCR2 antagonists function to inhibit the translocation of granulocytes (including neutrophils) out of the marrow and into circulation (and, inhibit translocation of MDSCs into tumors) [Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, Morse E 2014]. As expected, the class of CXCR2 antagonists demonstrates a mechanism-based decrease in circulating neutrophils. Therefore, the neutrophil count serves as an easily monitorable functional biomarker assay. Navarixin clinical trials have demonstrated a dose-dependent decrease in neutrophils, suggesting the molecule is sufficient to test the hypothesis: CXCR2 antagonism, in combination with pembrolizumab, improves outcomes for cancer patients relative to pembrolizumab alone.

MDSCs are present and active in a number of different tumor types [David JM, Dominguez C, Hamilton DH, Palena C. 2016] [Kumar V, Patel S, Tcyganov E, Gabrilovich DI. 2016]. Likewise, CXCR2 is expressed in a diverse set of tumors. Recent data suggest that CXCR2 antagonism might reverse tumor immune suppression caused by MDSCs [Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, Morse E 2014] [Theivanthiran B, DeVito NC 2017]. In addition, antagonism of CXCR2 has been shown to inhibit tumor metastasis and neo-angiogenesis in preclinical models. CXCR2 inhibition in combination with immunotherapy shows enhanced anti-tumor activity (anti-PD-1/anti-CTLA-4) in a preclinical prostate model [Lu X, Horner JW, Paul E, Shang X, Troncoso P, Deng P 2017]. CXCR2 inhibition enhances T cell entry, suppresses metastases, and confers sensitivity to anti-PD-1 treatment in KPC PDAC model. In addition, disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD-1 efficacy in a syngeneic RMS tumor models. Moreover, data indicates that navarixin treatment can enhance the anti-tumor activity of PD-1 blockade in a B16-F10 syngeneic tumor model that shows modest activity to anti-PD-1 as a monotherapy (complete responses observed in the combination arm).

No studies with navarixin have been initiated in oncology indications. However, it was previously developed by Schering for non-oncology indications (chronic obstructive pulmonary disease [COPD], asthma, psoriasis). As a result of this development, over 900 subjects were treated with navarixin in clinical trials. Several Phase II studies were conducted in COPD, asthma, and psoriasis. No impact of treatment was observed in the psoriasis study. Two small asthma studies showed trends to clinically significant results.

The largest Phase II trial was a proof of concept (POC) study in patients with moderate to severe COPD in which navarixin 50 mg was compared with placebo. Navarixin treatment led to statistically significant improvement in forced expiratory volume (FEV) in patients with COPD who were current smokers. Treatment discontinuations for Grade 2 neutropenia were observed. No increases in infections or fevers were observed in treated patients versus the placebo group. Navarixin development was discontinued due to the modest and restricted (current smokers) observed benefit.

Multiple Phase I studies in healthy volunteers confirm that navarixin induces a dose dependent peripheral reduction in neutrophils; 24% and 48% median ANC decrease for 30 and 100 mg respectively. Neutrophil migration from the marrow is inhibited, and no marrow hypo-cellularity was observed. The neutrophil reduction is rapidly reversible on dosing cessation, and peripheral neutrophils return to baseline values in 48-96 hours without cytotoxic or myelosuppressive effects on the bone marrow.

Several CXCR2 antagonists are under development. AstraZeneca has reported AZD5069 Phase 1 results in combination with durvalumab [Steele CW, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R 2016]. The combination is reported to be well-tolerated, and the AZD5069 combination with durvalumab does not appear to enhance toxicities observed from either AZD5069 or durvalumab monotherapies.

Navarixin development will focus on combinations with immune checkpoint inhibitors (pembrolizumab). The removal of the immune suppression induced by navarixin, combined with immune checkpoint abrogation, is hypothesized to improve cancer therapy outcomes relative to either treatment alone. The mechanistic, dose-dependent, rapidly reversible, decrease in peripheral neutrophils induced by navarixin (and all CXCR2 antagonists) will serve as a readily monitorable pharmacodynamic marker in this trial.

3.2.1.2 Pembrolizumab (MK-3475) Pharmaceutical and Therapeutic Background

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.

3.3 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 participants participating in this clinical study may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

4. Objectives/Hypotheses and Endpoints

Male/female participants of at least 18 years of age with selected advanced/metastatic solid tumors will be enrolled in this study.

Objective	Endpoint
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) following administration of navarixin in combination with pembrolizumab.	• Objective response is a confirmed complete response (CR) or partial response (PR).
• Objective: To determine the safety and tolerability of navarixin in combination with pembrolizumab.	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study treatment due to an AE.
Secondary	
• Objective: To evaluate objective response rate (ORR) as assessed by investigator based on iRECIST (modified RECIST 1.1) [Seymour, L., et al 2017], progression-free survival (PFS) as assessed by investigator based on RECIST 1.1 and iRECIST, and overall survival (OS) following administration of navarixin in combination with pembrolizumab	• Objective response is a confirmed CR or PR. • PFS is time from the first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first. • OS is time from the first dose of study medication to death due to any cause.
• Objective: To evaluate the pharmacodynamics as measured by absolute neutrophil counts (ANC) following administration of navarixin in combination with pembrolizumab.	• ANC in 10^9/L
• Objective: To evaluate the pharmacokinetics (PK) of navarixin when administered in combination with pembrolizumab	• PK parameters including area under the curve (AUC) in ng·hr/mL, maximum concentration (C_{max}) in ng/mL, trough concentration (C_{trough}) in ng/mL

Objective	Endpoint
Tertiary/Exploratory	
• Objective: To evaluate the development of circulating anti-pembrolizumab antibodies, as appropriate, following administration of navarixin in combination with pembrolizumab	• Anti- pembrolizumab antibody level
• Objective: To evaluate the relationship between navarixin PK and ANC	• ANC; navarixin PK parameters including AUC, C_{max}, and C_{trough}
• 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 of navarixin in combination with pembrolizumab.	• Germline genetic variation, genetic (deoxyribonucleic [DNA]) mutations from tumor, tumor and blood ribonucleic acid (RNA) variation, proteomics and immunohistochemistry (IHC), and other blood-derived biomarkers

5. Study Design

5.1 Overall Design

This is a stratified, parallel, 2-arm (2-dose), randomized, uncontrolled multicenter study of navarixin in combination with pembrolizumab in participants with selected advanced/metastatic solid tumors. The study will use a 2-stage adaptive design based on pre-specified criteria. There is no untreated/placebo comparator arm.

Participants with PD-(L)1 refractory NSCLC, CRPC, or MSS CRC will be randomized into one of two dose arms. In dose Arm A, participants will be treated with 30 mg orally QD navarixin. In dose Arm B, participants will be treated with 100 mg orally QD navarixin. Participants in both Arms A and B will be treated concomitantly with pembrolizumab 200 mg IV Q3W.

Per the interim safety analysis, if no more than 3 participants in the first 10 evaluable participants have experienced DLTs during the first cycle in an arm, this arm may be expanded by enrolling an additional 20 participants to complete Stage 1. However, during Stage 1, **if at any time >3 DLTs are observed within the first 10 evaluable participants**, enrollment into an arm will be discontinued.

In addition, the following stopping rule is included for excessive toxicity occurring outside the current defined DLT window. If 4 or more of the first 10 evaluable participants have a DLT per current protocol definition (either within the first cycle DLT observation window or outside this window) after they have all finished the first cycle observation, enrollment into the arm may be discontinued unless totality of the data (eg, including efficacy) supports a favorable risk-benefit trade-off.

Safety and tolerability will be continuously monitored throughout the study duration. If the regimen is deemed intolerable, the arm may be discontinued even if stopping rule is not met.

The overall design is an adaptive 2-stage design. In each arm, up to 30 participants will be enrolled in the first stage, and up to 30 participants in the second stage. In the first stage, 30 participants (with 10 per tumor type) will be enrolled in each arm (dose level). When all participants in a given arm with a given tumor type complete the first on-treatment scan at 9 weeks or when clinically indicated (see Section 9.2.1.2), a futility analysis will be conducted to determine whether that tumor type and arm will progress to Stage 2. If a tumor type passes the futility analysis (see Section 5.1.4) in Stage 1, at least 10 participants will be enrolled with that tumor type in the second stage.

Initial enrollment in each dose arm will be staggered. The first 3 participants in dose Arm A or dose Arm B will be enrolled no more frequently than 1 participant per week, to allow for peripheral neutrophil assessment between participants. Peripheral neutrophil assessment (ANC) will occur at baseline, Day 3, and Day 8 during the first cycle for all participants. Decreased ANC counts typically return to normal in 48-96 hours following dosing cessation. Standard support for oncology patients with low ANC will be considered as appropriate. See dose reduction algorithm (Section 7.2.1) for more information.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Study SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Study Diagram

The study design is depicted in Figure 1.

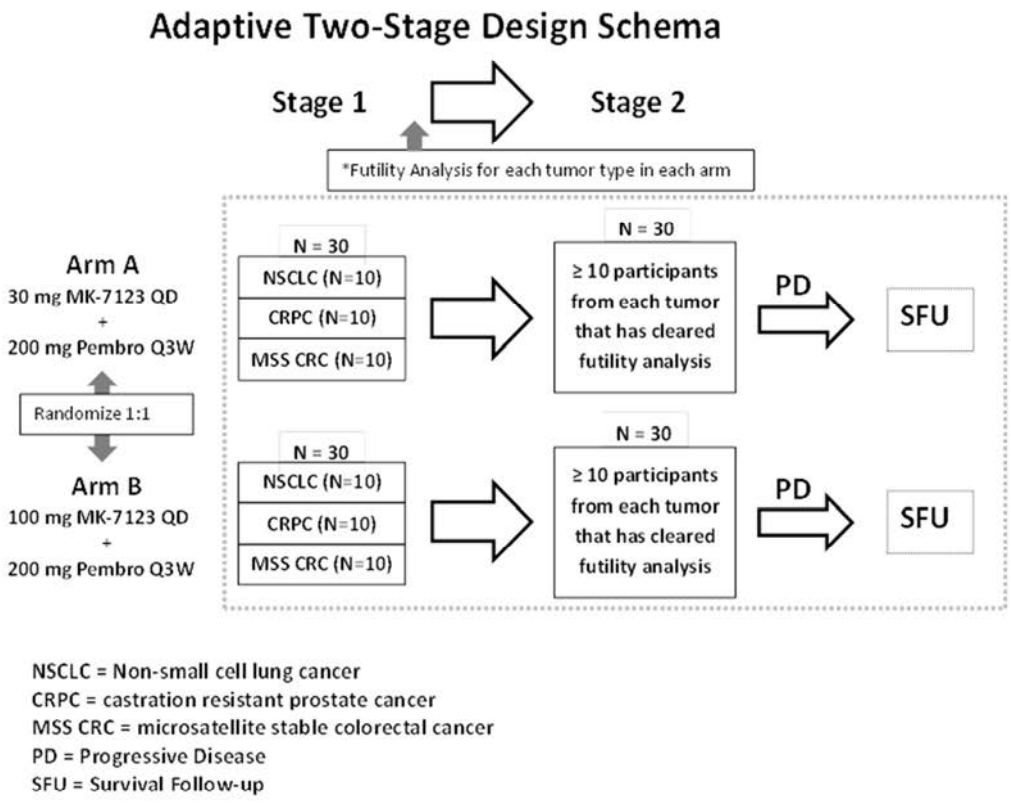

Figure 1 Study Design

Guidance for dose decision and expansion is depicted in Figure 2.

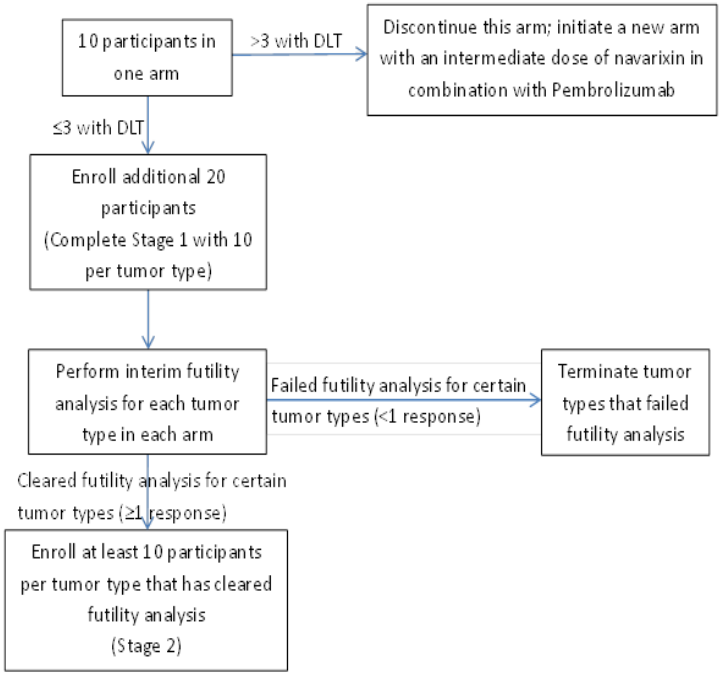

Figure 2 Guidance for Dose Decision and Expansion

5.1.2 Evaluation of Safety

In order 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 prior to completing all the safety evaluations in Cycle 1 for reasons other than treatment-related adverse events.
- They receive <75% of the total MK-3475 (or pembrolizumab) infusion and/or navarixin in Cycle 1 (eg, if the infusion had to be discontinued due to an infusion reaction) and they did not experience a DLT.

5.1.3 Dose Limiting Toxicity

Formal DLT evaluation will be performed at the interim safety analysis, following completion of one cycle of treatment by 10 evaluable participants in each dose arm. DLT nonevaluable participants will not be replaced. For example, if one 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 one cycle (Day 1 to Day 21. Day 1 is considered the date a study drug 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 G-CSF will not be allowed.

An arm dose will be considered intolerable if >3 of 10 evaluable participants experience DLTs in Cycle 1. If the arm dose is not tolerated at 30 mg (and 100 mg), the arm may be discontinued and the protocol may be amended to include a lower navarixin dose.

All toxicities will be graded based on investigator assessment (Appendix 4 "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 non-hematologic toxicity (not laboratory)
2) Grade 4 anemia of any duration
3) Grade 3 anemia lasting >7 days or requiring transfusion
4) Grade 4 hematologic toxicity (other than anemia) lasting ≥7 days, except thrombocytopenia
    a) Grade 4 thrombocytopenia of any duration
    b) Grade 3 thrombocytopenia associated with bleeding
5) Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.
6) Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Medical intervention is required to treat the participant, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >72 hours.

    Exceptions:
    - Clinically non-significant, treatable, or reversible laboratory abnormalities including uric acid

7) Any of the following liver test abnormalities are observed (Hy's Law):
    - ALT or AST > 3X ULN with TBL > 2X ULN with no elevation in alkaline phosphatase (AP < 2X ULN)
    - No other reasons can be found to explain the combination of increased aminotransferase(s) (AT) and TBL, such as viral hepatitis, A, B, or C, preexisting or acute liver diseases, or another drug capable of causing the observed injury
8) Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4°) for more than one hour.
9) Inability to administer ≥75% of the planned navarixin dose due to drug-related tolerability.
10) Delay in starting Cycle 2 by >2 weeks due to toxicity.

5.1.4 Futility Analysis

An interim futility analysis for efficacy will be performed after the first 10 participants for each tumor type have at least 1 post-baseline scan assessment in each dose arm in Stage 1. If one or more responses (confirmed or unconfirmed) are observed for a tumor type in an arm (i.e. ≥10% response rate), this tumor type may be expanded to enroll at least additional 10 participants in Stage 2, for a maximum enrollment of 60 participants in this arm across 3 tumor types. Otherwise, this tumor type may be stopped early for futility.

If the decision is made to expand a tumor type in dose Arm A to Stage 2, this tumor type in dose Arm B may be expanded to Stage 2 as well, irrespective of the number of responses as long as it has passed the safety evaluation. While the decision rule is mainly based on confirmed and unconfirmed responses, the totality of data will also be taken into account.

5.2 Number of Participants

Greater than or equal to 120 participants will be randomized in order to achieve 120 evaluable participants as per Section 10. If no efficacy is noted in any tumor types the total number may be as low as 60.

5.3 Beginning and End of Study Definition

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

5.3.1 Clinical Criteria for Early Study Termination

Early study termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug. In the event of the Sponsor decision to no longer supply study drug, ample notification will be provided to the sites so that appropriate adjustments to participant treatment can be made.

5.4 Scientific Rationale for Study Design

This Phase 2 study is being conducted to evaluate the efficacy, safety, and tolerability of navarixin in selected solid tumors when administered in combination with pembrolizumab. Two different doses of navarixin (30 mg and 100 mg QD) will be evaluated in combination with the standard dose of pembrolizumab (200 mg Q3W).

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

A primary objective for this trial is to evaluate the antitumor activity of navarixin in combination with pembrolizumab in participants with selected advanced or metastatic solid tumors. Tumor response (ORR) in participants with solid tumors will be assessed using RECIST 1.1 based on investigator assessment. Images will be collected for possible analysis by blinded, independent central review.

ORR will be used for decision making. A time to event endpoint (e.g., PFS, OS) would require a control group (preferably placebo controlled, blinded). Given that the participants in this study have refractory disease, and have disease that is not responsive to PD-1 antagonists, ORR is considered evidence of efficacy, and has formed the basis for accelerated approval (for oncology agents) in the US.

Immunotherapeutic agents such as navarixin 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 typical cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a comprehensive response assessment of immunotherapeutic agents such as navarixin and pembrolizumab. Therefore, as a secondary objective, ORR will also be assessed by iRECIST.

Additional secondary objectives include evaluation of PFS by RECIST 1.1 and iRECIST and OS of participants treated with navarixin in combination with pembrolizumab.

For additional details about assessing efficacy endpoints using RECIST 1.1 and iRECIST, see Appendix 7 in Section 12.

5.4.1.2 Safety Endpoints

A primary objective of this trial is to characterize the safety and tolerability of navarixin in participants with advanced/ metastatic solid tumors when administered in combination with pembrolizumab. The primary safety analysis will be based on participants who experience toxicities as defined by CTCAE Version 4.0.3 criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received navarixin in combination with pembrolizumab.

Safety parameters commonly used for evaluating investigational systemic anti-cancer treatments are included as safety endpoints for the study including, but not limited to, the incidence of, causality to, and outcome of AEs/SAEs; changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 4.0.3.

5.4.1.3 Pharmacokinetic Endpoints

A secondary objective of this study is to characterize the PK profile of navarixin and pembrolizumab following administration of navarixin in combination with pembrolizumab. The systemic concentrations of these agents will serve as the primary readout for the PK, and these data will be used to derive PK parameters for these agents when administered in combination. Furthermore, the results of these analyses will be used in conjunction with the PD, safety, and exploratory endpoint data to help assess future dosing strategies for navarixin.

5.4.1.4 Pharmacodynamic Endpoints

Existing data from prior clinical studies for respiratory therapies indicate that navarixin causes a dose-dependent decrease in neutrophils. While this may limit dosing, its target-mediated nature (CXCR2 mediates neutrophil trafficking) and existence of available clinical data also make it a suitable biomarker for target modulation due to navarixin activity. In addition, reports from competitors (AZD5069) [Steele CW, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R 2016] support the mechanism-based observed ANC reduction observed after navarixin blockade of CXCR2 signaling. Absolute neutrophil counts (ANC) will be used to evaluate target engagement/modulation and its relationship to pharmacokinetics endpoints. In addition, ANC levels will be closely monitored during the course of the trial to identify if there are any instances of neutropenia that may affect participant safety.

5.4.1.5 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of anti-tumor agents. However, the mechanism of action of these 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 identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide therapies 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, single-nucleotic polymorphism [SNP] analyses, whole exome sequencing, whole genome sequencing)

This research will 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. 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 immune-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).

Tumor/blood RNA analysis: Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and/or blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab in combination with navarixin or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing IFN-γ transcriptional pathways) may be evaluated and new signatures may be identified. In addition, expression levels of the targeted receptor CXCR2 and correlation to response may also be investigated. MicroRNA profiling may also be pursued.

Immunohistochemistry (IHC) in tumor biopsies: Mechanistic studies carried out in preclinical models of melanoma (B16-F10) and colon carcinoma (CT26) showed a significant reduction in granulocytic MDSC infiltration in tumors after navarixin treatment. IHC in tumor biopsies will be used to assess changes in myeloid and lymphoid cell content in tumor biopsies as a result of navarixin treatment. In addition, PD-L1 status by IHC will also be determined.

Participants will be required to provide an archival tumor tissue sample and/or a fresh biopsy of tumor before treatment for these biomarker analyses. Participants will also be asked to agree to a biopsy of tumor after initiation of study treatment and to provide the acquired tissue for these biomarker analyses.

Other blood/serum derived biomarkers: In addition to expression within the tumor tissue, tumor-derived proteins can be shed from tumor and released into the blood. In the case of proteins, enzyme-linked immunosorbent assays can measure such proteins in serum and plasma and correlate this expression with response to pembrolizumab plus navarixin combination therapy. Previous clinical trials (P05575) and published competitor data have reported concentration changes in the CXCR2 ligands GRO-α and IL-8, and in the neutrophil-associated enzyme MMP-9, after pathway blockade. In addition, changes in serum IL-8 levels have been shown to reflect and predict response to anti-PD-1 treatment in melanoma and NSCLC .Changes in IL-8, GRO-a, and MMP-9 concentrations as a result of combination therapy will be evaluated by enzyme-linked immunoassay.

5.4.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

5.4.1.6 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 (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 sub-study are presented in Appendix 2 – Collection and Management of Specimens for Future Biomedical Research.

5.5 Justification for Dose

5.5.1 Starting Dose for This Study

An exposure response (ER) analysis from previous clinical experience was conducted to establish the relationship between navarixin AUC and % reduction in absolute neutrophil count (ANC – functional biomarker of navarixin activity) from baseline. The ER analysis revealed a dose-dependent decrease in neutrophils. The 30 mg and 100 mg doses were chosen as there was a clear differentiation in % ANC reduction between the 2 doses and the % ANC reduction corresponding to exposures at the 100 mg dose were at the plateau of the ER relationship. The low dose (30 mg PO QD) induced a moderate decrease in circulating neutrophils, while the higher dose (100 mg PO QD) induced a greater reduction.

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and 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 overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [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 vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 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 (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 (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, 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.

5.5.2 Maximum Dose/Exposure for This Study

The maximum pre-planned dose of navarixin that will be used in this study is 100 mg QD. Evidence from the percent ANC reduction versus dose data suggests that the 100 mg dose is near the plateau of the exposure response relationship. Higher doses may be considered if supported by clinical PK/PD and efficacy data.

5.5.3 Rationale for Dose Interval and Study Design

Navarixin

Multiple doses of up to 50 mg navarixin, administered for up to 12 weeks in participants with moderate-to-severe COPD, were found to be safe and well-tolerated. Multiple doses of navarixin, 30 mg QD, administered for up to 10 days in participants with mild asthma and up to 4 weeks in participants with severe asthma, were found to be safe and well tolerated. The effect of navarixin on ANCs was similar following both the single-dose and multiple doses. At 24 hours post dosing, the median percent ANC reduction for 30 and 100 mg navarixin (orally) was 24% and 48%, respectively. There were no other significant changes in clinical laboratory parameters, vital signs, and electrocardiograms.

Navarixin, 30 mg QD, significantly reduced ANCs and sputum neutrophils in participants with COPD, along with early signs of clinical improvement. Navarixin, 30 mg QD, resulted in a significant reduction in ANCs and sputum neutrophils in participants with severe asthma and demonstrated an improvement in asthma control, as well as a reduction in the rate of mild asthma exacerbations. Single dose administration of 100 mg navarixin in healthy volunteers was safe and well tolerated in healthy participants. Multiple doses of 100 mg navarixin administered QD for up to 14 days in healthy participants was safe and well

tolerated. There was a significant but reversible decline in ANCs after both single and multiple doses of 100 mg.

While preliminary signals of clinical benefit were observed in navarixin-treated asthma and COPD patients, this efficacy was not sufficient to warrant continued development in these indications.

Following multiple daily oral administration of 10, 30, 50, and 100 mg navarixin, plasma concentration steady state was achieved by Day 11; navarixin minimum observed plasma concentration (C_{min}) values were similar on Days 11 through 14. There was little to no accumulation of navarixin observed in plasma on Day 14 with mean accumulation ratio (R) values ranging from 1.05 to 1.21.

Pembrolizumab

The planned dose and dosing interval of pembrolizumab for this study is 200 mg every 3 weeks (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 and regardless of tumor types.

No pembrolizumab dose modifications are planned for this study.

6. Study Population

Male and female participants of at least 18 years of age, with selected advanced/metastatic solid tumors (NSCLC [PD-(L)1 refractory], CRPC, and 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.

6.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics – All Participants

1. Have one of the following histologically- or cytologically-confirmed advanced/metastatic (diagnosis of Stage IV [AJCC version 8 or current version as applicable]) solid tumors (NSCLC, CRPC, or MSS CRC) by pathology report and have received, or been intolerant to, or have been ineligible for all treatment known to confer clinical benefit.
2. Have Stage III or Stage IV disease that is not surgically resectable.
3. Have measureable disease by RECIST 1.1 criteria as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measureable if progression has been demonstrated in such lesions.
4. Have supplied tumor tissue from either a newly obtained biopsy or an archival specimen from a site not previously irradiated for biomarker analysis.

Non-small cell lung cancer (NSCLC) Participants Only

5. Have a histologically or cytologically confirmed diagnosis of Stage IV metastatic NSCLC.
6. Stage IV metastatic NSCLC tumors that are PD-(L)1 positive (TPS ≥50%), do not harbor EGFR-sensitizing mutations and ALK translocations that are amenable to treatment with respective tyrosine kinase inhibitor therapy, and who have received prior treatment with a PD-(L)1 antagonist
7. Must have progressed on treatment with an anti-PD-(L)1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:
    a. Has received at least 2 doses of an approved anti-PD-(L)1 mAb.
    b. Has demonstrated disease progression after anti-PD-(L)1 as defined by RECIST 1.1 The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than 4 weeks from the date of the first documentation of PD in the absence of rapid clinical progression.(This determination will have been made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression).
    c. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-(L)1 mAb.

Castration Resistant Prostate Cancer (CRPC) Participants Only

8. Have histologically- or cytologically-confirmed (if acceptable according to local health authority regulations) adenocarcinoma of the prostate. Components of small cell prostate cancer are permitted. Diagnosis must be stated in a pathology report and confirmed by the investigator.
9. Have prostate cancer progression on the most recent treatment, as determined

    by the investigator, by means of one of the following:

    a. PSA progression using local laboratory values as defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each assessment where the PSA value at screening should be ≥2 ng/mL
    b. Radiographic disease progression in soft tissue based on RECIST 1.1 criteria with or without PSA progression.
    c. Radiographic disease progression in bone defined as the appearance of 2 or more new bone lesions on bone scan with or without PSA progression.

        Note: Radiographs must be collected and transmitted to the central imaging vendor at study entry.

10. Must have progressed on at least one second generation anti-androgen therapy (e.g., enzalutamide, abiraterone) according to PCWG3 guidelines.
11. Have ongoing androgen deprivation with serum testosterone <50 ng/dL (<2.0 nM).
    a. If the participant is currently being treated with luteinizing hormone-releasing hormone agonists or antagonists (participants who have not undergone an orchiectomy), this therapy must have been initiated at least 4 weeks prior to first dose of trial treatment and treatment must be continued throughout the study.

Microsatellite Stable Colorectal Cancer (MSS-CRC) Participants Only

12. Have a histologically proven locally advanced unresectable or metastatic (Stage IV) CRC.
13. Have locally confirmed microsatellite stable (MSS) CRC; participants with microsatellite instability-high (MSI-H) or microsatellite unstable CRC are not eligible.
14. Have been previously treated with standard therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan.
    a. Participants who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also 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 following treatment.

Demographics – All Participants

15. Men and women who are ≥18 years of age.
16. Have an ECOG performance status of 0 or 1.

Male participants:

17. A male participant must agree to use contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

Female participants:

18. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

    a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3

    OR

    b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days after the last dose of study treatment.

Informed Consent

19. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study. The participant may also provide consent/assent for Future Biomedical Research. However the participant may participate in the main study without participating in Future Biomedical Research.

Laboratory Values – All Participants

20. Demonstrate adequate organ function as defined by the following table (Table 1).

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	>1,500/mcL
Platelets [a]	>100,000/mcL
Hemoglobin [a]	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **or** creatinine clearance (CrCl) (measured **or** calculated) [b] **or** Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X upper limit of normal (ULN) **or** ≥60 mL/min for participant with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN or Direct bilirubin ≤1.5 X ULN for participants with total bilirubin levels >1.5 X ULN; if there is no institutional ULN, then direct bilirubin must be <40% of total bilirubin to be eligible. Note: In no case can the total bilirubin exceed 3 X ULN.
Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)	≤2.5 X ULN or ≤5 X ULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) **or** Prothrombin Time (PT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

System	Laboratory Value
[a] Criteria must be met without packed red blood cell (pRBC) transfusion within last 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months). [b] Creatinine clearance (CrCl) should be calculated per institutional standard. If no local guideline is available, creatinine clearance should be calculated using the Cockcroft-Gault Method: CrCl = ([140-age] * weight [kg] * [0.85 for females only]) / (72 * serum creatinine) 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.	

6.2 Exclusion Criteria

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

Medical Conditions

1. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years.

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

2. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
3. Has had a severe hypersensitivity reaction to treatment with any monoclonal antibody or components of the study drug(s).
4. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) 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. In addition to active autoimmune disease, participants who have previously been permanently discontinued from PD-(L)1 therapy due to immune related side effects are not eligible for the study.
5. Has an active infection requiring systemic therapy.
6. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoracocentesis or paracentesis) is eligible.
7. Has interstitial lung disease that required oral or intravenous glucocorticoids to assist with management.

8. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
9. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years.

   Note: Participants who have had a stem cell transplant >5 years ago are eligible as long as there are no symptoms of graft-versus-host disease (GVHD).
10. Has a known history of human immunodeficiency virus (HIV) infection.

    Note: No HIV testing is required unless mandated by local health authority.
11. Has 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. Has a history or current evidence of a gastrointestinal (GI) condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) or impaired liver function or diseases that in the opinion of the Investigator may significantly alter the absorption or metabolism of oral medications; 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 drugs hazardous, or make it difficult to monitor adverse effects such that it is not in the best interest of the participant to participate, in the opinion of the treating Investigator.
13. Has known psychiatric or substance abuse disorders that would interfere with the participant's ability to cooperate with the requirements of the study.
14. Is pregnant or expecting to conceive or father children within the projected duration of the study.
15. Has undergone major surgery and has not recovered adequately from any toxicity and/or complications from the intervention prior to starting study therapy.
16. A WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of study treatment (see Appendix 3). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Prior/Concomitant Therapy

17. Participants with CRPC or MSS CRC who have received prior therapy with an anti-PD-1, anti-PD-(L)1, or anti PD L2 agent.
18. Have been treated with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137).

19. Has received prior systemic anti-cancer therapy including investigational agents or has used an investigational device within 28 days prior to the first dose of study treatment. 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 immune-related adverse events (eg, thyroid replacement therapy) will not be excluded from participation in this study.
20. Has received prior radiotherapy (not to target lesions) within 2 weeks of start of study treatment. 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.
21. Is expected to require any other form of antineoplastic therapy while on study.
22. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy in excess of replacement doses (prednisone ≤10 mg/day is acceptable), or on any other form of immunosuppressive medication.

    Note: The use of physiologic replacement doses of corticosteroids may be approved after consultation with the Sponsor Medical Monitor or designee.
23. Has received a live-virus vaccine within 30 days prior to first dose of study medication. Vaccines that do not contain live virus are permitted.

Prior/Concurrent Clinical Study Experience

24. Had been previously treated with a CXCR2 inhibitor (eg, AZD5069, reparixin, danirixin, LY3041658 Ab, HuMax-IL8, etc.)

6.3 Lifestyle Restrictions

There are no lifestyle restrictions.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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 adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the data entry guidelines.

6.5 Participant Replacement Strategy

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

7. Treatments

Study treatment is defined as any investigational treatment(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 treatment(s) provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatments to be used in this study are outlined below in Table 2 Study Treatment(s).

Table 2 Study Treatment(s)

Study Treatment Name:	Navarixin (MK-7123)	Pembrolizumab (MK-3475)
Dosage Formulation:	Oral dry filled capsule	Solution for Infusion
Unit Dose Strength(s):	Two potencies: 10-mg and 50-mg capsules	100 mg/vial
Dosage Level(s):	30 mg QD 100 mg QD	200 mg Q3W
Route of Administration:	Oral	IV infusion
Sourcing:	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.

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 as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 9.1.8 for details regarding administration of the study treatment.

7.2 Dose Modification

7.2.1 Navarixin Dose Modification

For Grade 4 ANC, or febrile neutropenia (Grade 3 or 4 ANC), navarixin will be held for 1 week to allow the ANC to recover. ANC will be measured for recovery at 1 week (local draw is permissible). If ANC has recovered to Grade 1 or better, the participant will be restarted at a lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the dose arm. If the participant has not recovered, he/she will return to the clinic in one week for a second ANC draw. If ANC has recovered to Grade 1 or better, the participant will be restarted at a lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the arm. If not recovered, he/she will discontinue navarixin, but remain on pembrolizumab treatment. There will only be one dose reduction per arm. If the participant experiences Grade 4 ANC or febrile neutropenia while already dosed reduced, the participant will discontinue navarixin treatment (Table 3).

For immune related AEs, see Section 7.2.2 for pembrolizumab dosing instructions. If pembrolizumab dosing is held, navarixin dosing should also be held. If pembrolizumab dosing is resumed, navarixin dosing may be restarted at a lower dose. If navarixin has already been dose reduced, then navarixin should be discontinued Table 3 and Section 7.2.2).

For DLTs (Section 5.1.3) not encompassed under irAEs (Section 7.2.2), both navarixin and pembrolizumab will be held for 1 week (an additional extension period for recovery of the toxicity may be allowed, following consultation with the Sponsor and the investigator). Then, if toxicity has recovered to Grade 1 or better (or participant's baseline value), participant will be restarted on the standard dose of pembrolizumab and a lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the dose arm. There will only be one navarixin dose reduction per arm. Therefore, if the participant experiences the DLT while already dosed reduced, the participant will discontinue navarixin, but may restart the standard dose of pembrolizumab following recovery (Table 3).

Table 3 Navarixin/Study Drug Dose Modifications

Toxicities	Navarixin Dosing	Action
Grade 4 ANC	Hold navarixin for 1 week for ANC to recover.	• If ANC recovered to Grade 1 or better, participant will be restarted at lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the arm. • If ANC has not recovered, participant will receive a second ANC test after an additional 1 week ▪ If ANC recovered to Grade 1 or better, participant will be restarted at lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the arm. ▪ If ANC has not recovered, participant will discontinue navarixin treatment, but will continue to receive pembrolizumab treatment.
Febrile neutropenia (Grade 3 or 4 ANC)	Hold navarixin for 1 week for ANC to recover.	• If ANC recovered to Grade 1 or better, participant will be restarted at lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the arm. • If ANC has not recovered, participant will receive a second ANC test after an additional 1 week ▪ If ANC recovered to Grade 1 or better, participant will be restarted at lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the arm. ▪ If ANC has not recovered, participant will discontinue navarixin treatment, but will continue to receive pembrolizumab treatment.

Toxicities	Navarixin Dosing	Action
Grade 4 ANC or febrile neutropenia while navarixin already dosed reduced	There will be only 1 dose reduction per arm.	• Participant will discontinue navarixin.
	Study Medication Dosing	
Immune related AEs (irAEs) which require pembrolizumab dose modification (See Section 7.2.2)	Follow Section 7.2.2 for pembrolizumab dosing instructions. Hold navarixin while pembrolizumab is held to allow irAE to recover.	• Hold/discontinue pembrolizumab dosing according to instructions in Section 7.2.2 • Hold navarixin while pembrolizumab is held. • If pembrolizumab is restarted, restart navarixin at lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the arm. • If navarixin has already been dose reduced, discontinue navarixin.
DLTs not described above (see Section 5.1.3)	Hold navarixin for 1 week* for DLT to recover. Hold pembrolizumab while navarixin is held. *An additional extension period for recovery of the toxicity may be allowed, following consultation with the Sponsor and the Investigator.	• If toxicity has recovered to Grade 1 or better (or participant's baseline value), participant will be restarted at lower dose of navarixin (ie, from 100 mg to 50 mg or from 30 mg to 20 mg), depending on the arm. If navarixin has already been dose reduced, discontinue navarixin. Pembrolizumab will be restarted at normal dose. • If toxicity has not recovered, participant will discontinue study treatment (discontinue both pembrolizumab and navarixin).

7.2.2 Pembrolizumab Dose Modification

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with 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 pembrolizumab has been withheld, 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 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.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/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		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. 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		

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 pembrolizumab has been withheld, 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 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.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/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	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		

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 pembrolizumab has been withheld, 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 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.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

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 pembrolizumab has been withheld, 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 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.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	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 discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

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

7.3 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to dose Arm A and dose Arm B, respectively.

7.3.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

Tumor type (NSCLC [PD-(L)1 refractory], CRPC, and MSS CRC)

7.4 Blinding

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

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

Details on preparation and administration of navarixin (and pembrolizumab) are provided in the appropriate Pharmacy/Procedures Manual

7.5.2 Handling, Storage and Accountability

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment 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 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 treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

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

7.7 Concomitant Therapy

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

- Immunotherapy not specified in this protocol
- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy (radiotherapy for symptom management is allowed)
- Live vaccines within 28 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid vaccines. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids other than to modulate symptoms from an immune-mediated AE. Chronic systemic replacement doses of steroids and non-systemic steroids including inhaled steroids, topical steroids, intra-nasal steroids, intra-articular, and ophthalmic steroids are allowed.

There are no prohibited therapies after the Post-Treatment Safety Follow-Up visit.

7.7.1 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 7.2, (Table 4). 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.

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) in Section 7.2.1 for guidelines regarding navarixin dose modification and supportive care. Refer to Section 7.2.2 for pembrolizumab dose modification.

Supportive Care Guidelines for Pembrolizumab

Pneumonitis:

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and bowel perforation (such as peritoneal signs and ileus).

- All participants who experience 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. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists >3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists >1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA):

- For **T1DM** or **Grade 3-4 hyperglycemia**
  - Insulin replacement therapy is recommended for Type 1 diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatic:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks

Renal Failure or Nephritis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Myocarditis:

- For **Grade 1 or 2** events, withhold. Based on severity of AE administer corticosteroids. Ensure adequate evaluation to confirm etiology and/or exclude other causes.

- For **Grade 3 and 4** events, permanently discontinue. Based on severity of AE administer corticosteroids. Ensure adequate evaluation to confirm etiology and/or exclude other causes.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 5 shows treatment guidelines for participants who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Pembrolizumab Infusion Reaction 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 infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion and monitor symptoms.** 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 one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	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. **Participant is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

7.9 Clinical Supplies Disclosure

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

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment 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 treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - Schedule of Activities and Section 9.11.3 – Post Study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Discontinuation and Withdrawal.

A participant must be discontinued from study treatment 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 treatment.
- 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 which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum or urine pregnancy test (depending on local regulation).

8.2 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 9.1.9 – Withdrawal/Discontinuation.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 8.3.

8.3 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, phone 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 pre-specified statistical data handling and analysis guidelines.

9. 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 assuring 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 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, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required is outlined in the Procedure Manual.

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

9.1 Administrative and General Procedures

9.1.1 Informed Consent

The investigator or qualified designee 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 qualified designee must ensure the appropriate consent is in place.

9.1.1.1 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 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.

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or 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 sub-study. A copy of the informed consent will be given to the participant.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study.

9.1.3 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 utilized 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 treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

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

9.1.4 Medical History

9.1.4.1 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 prior to enrollment. Details regarding the cancer under study will be recorded separately and not listed as medical history.

9.1.4.2 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.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 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 the first dose of study medication. 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.

9.1.5.2 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.

9.1.5.3 Concomitant Medications

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

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 9.3.

Any new anti-cancer 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.

9.1.6 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 one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.11.1.

9.1.7 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.

9.1.8 Treatment Administration

Study treatment should start on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

9.1.8.1 Timing of Dose Administration

Navarixin may be administered at any time in relation to food intake. Navarixin should be taken at approximately the same time each day.

9.1.9 Discontinuation and Withdrawal

Participants who discontinue study treatment 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 adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3..

9.1.9.1 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.

9.1.10 Participant Blinding/Unblinding

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

9.1.11 Domiciling

Participants will not be domiciled.

9.1.12 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.

9.2 Efficacy Assessments

9.2.1 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 (SIM). 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.

9.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to 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 and can be assessed by the central imaging vendor.

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.

9.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator or the start of new anticancer treatment, withdrawal of consent, or death, 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 9.2.1.5), disease progression should be confirmed by the site 4 to 8 weeks after 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 9.2.1.5. 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 9.2.1.5

9.2.1.3 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 (±4 week 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 (±7 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.

9.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 (assessed by investigator) will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment).

9.2.1.5 iRECIST Assessment of Disease

The iRECIST method 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 7. 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. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

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 iRECIST confirmed radiographic progression (iCPD) as defined in Appendix 7, 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 Section 2 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 7, with additional details in the iRECIST publication [Seymour, L., et al 2017].

Guidance for imaging and treatment after first radiologic evidence of progressive disease is shown in Table 6 and for clinically stable participants in Figure 3.

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

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 that has been verified by BICR]	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment 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.

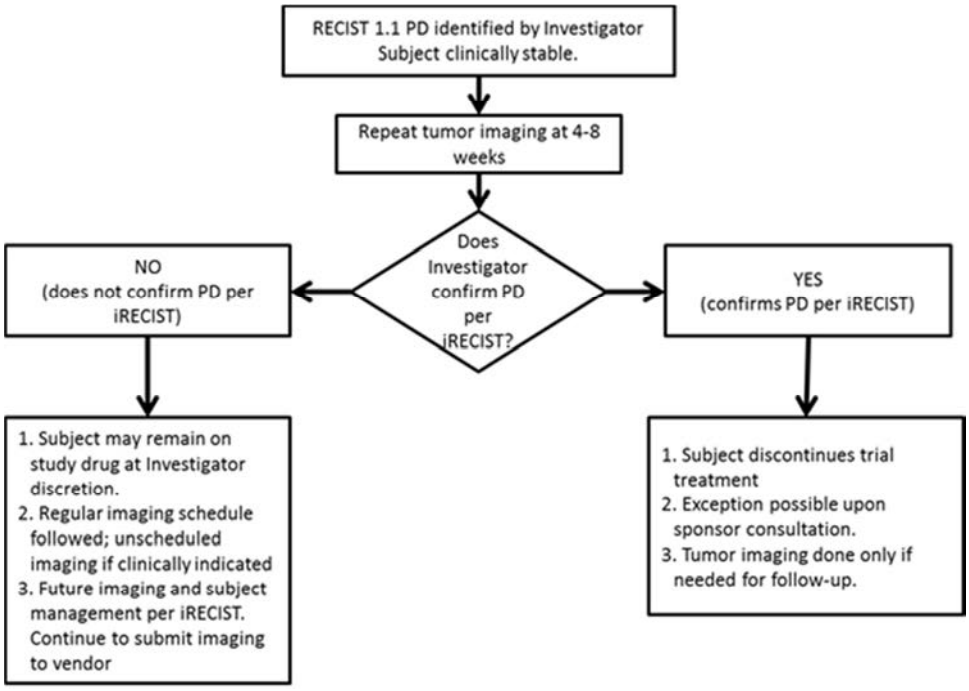

Figure 3 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigators

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

9.2.2 Prostate-Specific Antigen

The initial Prostate-Specific Antigen (PSA) biomarker assessment at screening must be performed within 28 days prior to the date of allocation.

In the first year (through Week 54), on study PSA biomarker assessments must be performed every 9 weeks (63 days ±7 days) from the date of allocation. After one year, participants who remain on-treatment will have PSA performed every 12 weeks (84 days ±7 days).

9.2.3 MSI Status in CPRC Patients

MSI status will be tested in participants with CRPC who demonstrate an objective response (either confirmed or unconfirmed) to therapy.

MSI status can be evaluated using the archival or newly obtained tumor tissue collected at screening.

9.3 Adverse Events (AE), Serious Adverse Events (SAE) and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (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 4.

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

AE, 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, who is a qualified physician, and any designees are responsible for detecting, assessing, 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 9.3.3.

Adverse events will not be collected for participants during the pre-screening 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.

9.3.1 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 treatment 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 treatment, or 30 days following cessation of study treatment 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 treatment, or 30 days following cessation of study treatment 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 to be 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 treatment 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 timeframes as indicated in Table 7.

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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

9.3.2 Method of Detecting AE, SAE 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 non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.3.3 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, 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 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 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 treatment 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 treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 9.3.1.

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

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

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, 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.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. an overdose of Sponsor's product, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

2. 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 may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

9.4 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for navarixin ≥200 mg and for pembrolizumab ≥1000 mg (ie, ≥5 times the indicated dose). No specific information is available on the treatment of overdose of navarixin and pembrolizumab. In the event of overdose, navarixin 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.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in Section 9.

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

9.5.1 Physical Examinations

9.5.1.1 Full Physical Exam

The Investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

9.5.1.1.1 Directed Physical Exam

For cycles that do not require a full physical exam as defined in Section 2, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs.

9.5.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to each pembrolizumab infusion, and during the follow-up period as specified in the Schedule of Activities.

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

9.5.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the Schedule of Activities in Section 2.0. Clinically significant abnormal findings at Screening should be recorded as medical history. Additional ECG(s) should be performed when clinically necessary.

9.5.4 Clinical Safety Laboratory Assessments

Refer to Appendix 5 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 5, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol 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 treatment, 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.

9.6 Pharmacokinetics

To evaluate the immunogenicity and exposure of pembrolizumab and exposure of navarixin in this indication, sample collections for analysis of anti-drug antibodies (ADA; anti-pembrolizumab antibodies) and PK are currently planned as shown in the Schedule of Activities. Blood samples for PK and ADA collected may be stored only at this time. Further analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

9.6.1 Blood Collection for Plasma Navarixin

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

Note: All pre-dose navarixin PK samples must be collected within 10 minutes prior to dosing.

9.6.1.1 Cycle 1

Samples will be collected on:

Day 1: Pre-dose (0), 1, 2, 4, and 6 hours, and 1 sample between 8 - 12 hours

Day 3: Pre-dose, and 1 sample between 6 - 12 hours

Day 8: Pre-dose, and 1 sample between 6 - 12 hours

9.6.1.2 Cycles 2 to 4

Samples will be collected on:

Cycle 2:

Day 1: Pre-dose (0), 1, 2, 4, and 6 hours, and 1 sample between 8 - 12 hours

Cycle 3:

Pre-dose (trough)

Cycle 4:

Pre-dose (trough)

9.6.1.3 After Cycle 4

Samples will collected according to the same schedule as for pembrolizumab PK samples.

9.6.2 Blood Collection for Pembrolizumab

Samples will be collected at pre-dose (trough) within 24 hours before infusion at Cycles 1, 2, 4, 6, and 8 and every 4 cycles thereafter.

9.7 Pharmacodynamics

Venous blood samples for safety and pharmacodynamics will be collected for measurement of neutrophil counts and neutrophil-to-lymphocyte ratios at pre-specified time points as outlined in the Schedule of Activities. Sample collection, storage, and shipment instructions for blood samples will be provided in the Procedures Manual.

As a safety lab, hematology (including ANC) will be collected on Day 1 of every cycle pre-dose as follows:

- On days when navarixin PK samples are collected, pre-dose ANC should be collected within 2 hours prior to dosing.
- On days when navarixin PK is **not** collected, pre-dose ANC can be collected within 24 hours prior to dosing.

In addition, for pharmacodynamic assessment, another sample will be collected between 6-12 hours after dosing on Days 1, 3, and 8 of Cycle 1, and Day 1 of Cycle 2.

9.8 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 in this study as specified in the SoA. Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the laboratory manual.

- Blood for Genetic Analysis
- Peripheral Blood Mononuclear Cell
- Blood for Immune Profiling (immunophenotyping)
- Blood for Serum Protein Analysis
- Blood for RNA Analyses
- Archival and/or Newly Obtained Tissue Collection

The Planned Genetic Analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the Future Biomedical Research consent. If the planned genetic analysis is

not approved, but Future Biomedical Research is approved and consent is given, this sample will be collected for the purpose of Future Biomedical Research.

9.9 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:

- DNA for future research
- Leftover cells from Peripheral Blood Mononuclear Cell
- Leftover serum from Serum Protein Analysis
- Leftover RNA from Blood for RNA Analyses
- Leftover main study tumor

9.10 Health Economics

Patient reported outcomes will not be assessed in this study.

9.11 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.11.1 Screening

Approximately 28 days prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1. Screening procedures may be repeated after consultation with the Sponsor.

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

- Laboratory tests are to be performed within 10 days prior to the first dose of study treatment. An exception is hepatitis testing which may be done up to 28 days prior to the first dose of study treatment if required.
- Evaluation of ECOG is to be performed within 7 days prior to date of randomization.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to 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 prior to 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.

9.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 2). Specific procedure-related details are provided in Section 9.1.

9.11.3 Post-Study

9.11.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first. If a participant discontinues from the treatment period approximately 30 days or later after the last dose of study treatment a separate Safety Follow-up visit does not need to be completed. The End of Treatment/Discontinuation visit should be completed only and include any assessments required at the Safety Follow-up visit but not the discontinuation visit.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

9.11.3.2 Disease Status 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 2) 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 anti-cancer therapy, disease progression, death, end of study. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

9.11.3.3 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.

9.11.4 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 prior to but not limited to an interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled 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).

10. 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 prior to 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.

10.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full details are in the Statistical Analysis Plan, Section 10.2 through Section 10.12.

Study Design Overview	Phase 2 trial of navarixin in combination with pembrolizumab in participants with selected advanced/metastatic solid tumors.
Analysis Populations	Efficacy (Primary and Secondary): Full Analysis Set (FAS) Safety (Primary): All Participants as Treated (ASaT) and DLT evaluable population PK and PD (Secondary): Per-Protocol (PP)
Primary Endpoint(s)	Efficacy: objective response is a confirmed complete response (CR) or partial response (PR). Safety: Dose-limiting toxicity (DLT) Adverse event (AE) Discontinuing study treatment due to an AE

Secondary Endpoint(s)	Objective response is a confirmed CR or PR. PFS is time from the first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first. OS is time from the first dose of study medication to death due to any cause. ANC in 10^9/L PK parameters of navarixin in combination with pembrolizumab and PK parameters of pembrolizumab in combination with navarixin, including area under the curve (AUC) in ng·hr/mL, maximum concentration (C_{max}) in ng/mL, trough concentration (C_{trough}) in ng/mL
Statistical Methods for Efficacy/ Pharmacokinetic/Pharmacodynamic Analyses	ORR will be estimated using an exact method based on the binomial distribution together with its 95% confidence interval (Clopper-Pearson interval). Methods for the secondary and exploratory efficacy analyses as well as the comparison between the two arms will be documented in an sSAP. PK parameters of study medicines will be summarized by planned visit and time for each arm. ANC and percent change from baseline in ANC will be summarized by planned visit and time for each arm separately.
Treatment Assignment	Participants will be randomized centrally through IVRS/IWRS to the 2 arms (doses) of navarixin in combination with pembrolizumab, stratified by tumor types.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate (e.g. counts, percentages). Miettinen and Nurminen's method will be used to estimate the difference between the 2 arms and its 95% confidence interval for number of participants with a DLT, number of participants with ≥1 AE and number of participants discontinuing study treatment due to an AE.
Interim Analyses	An interim safety analysis is planned for each arm after the first 10 participants across tumor types have finished at least one cycle of therapy in a given arm. An interim futility analysis is planned for each tumor type in each arm after the first 10 participants in each tumor type have finished the first tumor assessment. Additional interim 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	For the planning purpose, it is assumed that true objective response rates of <1% for MSS CRC and 5% for PDL1-refractory NCSLC and advanced prostate are not considered clinically meaningful, whereas true objective response rates of 16% for MSS CRC and 20% for PDL1-refractory NCSLC and advanced prostate or higher are. With 20 participants in each tumor type of each arm under the 2-stage adaptive design, the probability that the objective response rate of each tumor type is claimed clinical meaningful is <8% when the true response rate is not clinically meaningful and >75% when the true response rate is clinically meaningful. The total sample size is 60 participants per arm (20 per each tumor type in an arm). No formal hypothesis testing will be conducted.

10.2 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.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 4 – Objectives/Hypotheses and Endpoints.

10.4 Analysis Endpoints

10.4.1 Efficacy/Pharmacokinetics/Pharmacodynamic 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 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 9.2 – Efficacy Assessments.

Objective Response rate (ORR) is defined as the proportion of participants who achieve a confirmed complete response (CR) or partial response (PR).

Progression-free Survival (PFS) is defined as the time from the first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first.

Overall survival (OS) is defined as the time from the first dose of study medication to death due to any cause.

Pharmacokinetic endpoints include serum concentrations of navarixin and pembrolizumab, as well as derived PK parameters.

Pharmacodynamic endpoint includes ANC.

10.4.2 Safety Endpoints

The primary safety endpoint is the number/proportion of participants with DLTs (including participants with Grade 4 ANC decrease), and AEs, and who discontinue study treatment due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs.

A description of safety measures is provided in Section 9.5 - Safety.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will be used for the analyses of efficacy data in this study. It consists of all participants with a baseline scan that demonstrated measurable disease by the investigator's assessment, and who were administered at least 1 dose of study medicine.

10.5.2 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all participants who received at least 1 dose of study treatment.

The DLT evaluable population includes ASaT participants that meet the criteria for DLT evaluability (e.g., finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 5.1.3 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.

10.5.3 Pharmacokinetic Analysis Populations

The Per-Protocol (PP) population will be used for the analysis of PK and PD data in this study. The PP population consists of the subset of participants who complied 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.

10.6 Statistical Methods

This section describes the statistical methods that address the primary objectives. Methods related to secondary and exploratory objectives as well as the comparison between the t2arms will be described in the sSAP. The final analyses will be performed using data from both Stage 1 and Stage 2.

10.6.1 Statistical Methods for Efficacy Analysis

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

Methods for the secondary and exploratory efficacy analyses as well as the comparison between the two arms will be documented in the sSAP.

10.6.2 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, ECG measurements, and physical examinations.

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

Miettinen and Nurminen's method will be used to estimate the difference between the 2 arms and its 95% confidence interval for number of participants with a DLT, number of participants with ≥1 AE and number of participants discontinuing study treatment due to an AE.

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

10.6.3.1 Demographic and Baseline Characteristics

Demographic variables and baseline characteristics will be summarized.

10.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

Pharmacokinetic parameters of study medicines will be summarized by planned visit and time for each arm separately.

ANC and percent change from baseline in ANC will be summarized by planned visit and time for each arm separately.

Pharmacokinetics and pharmacodynamics modeling analyses will be documented in the sSAP.

10.7 Interim Analyses

There is one planned interim safety analysis and one planned interim futility analysis in this trial.

An interim safety analysis is planned for each arm after the first 10 participants across tumor types have finished at least one cycle of therapy in a given arm. If no more than 3 participants in the first 10 participants have experienced DTLs during the first cycle in a given arm, this arm may be expanded by enrolling 20 additional participants to complete Stage 1. Otherwise, this arm may be terminated due to safety concern.

An interim futility analysis is planned for each tumor type in each arm after the first 10 participants in each tumor type have at least 1 post-baseline scan assessment. If 1 or more

responses (ie, ≥10% response rate) are observed in a tumor type within an arm, this tumor type may be expanded to enroll at least 10 additional participants in Stage 2. Otherwise, this tumor type may be stopped early for futility. If the true response rate is 16%, there is an 82% chance to continue the study at the futility evaluation. If the true response rate is 20%, there is an 89% chance to continue the study at the futility evaluation.

Additional interim 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.

10.8 Multiplicity

There will be no multiplicity control in this study.

10.9 Sample Size and Power Calculations

For the planning purpose, it is assumed that true objective response rates of <1% for MSS CRC and 5% for PDL1-refractory NCSLC and advanced prostate are not considered clinically meaningful, whereas true objective response rates of 16% for MSS CRC and 20% for PDL1-refractory NCSLC and advanced prostate or higher are. With 20 participants in each tumor type of each arm under the 2-stage adaptive design, the probability that the objective response rate of each tumor type is claimed clinical meaningful is less than 8% when the true response rate is not clinically meaningful and more than 75% when the true response rate is clinically meaningful. The total sample size is 60 participants per arm (20 per each tumor type in an arm). No formal hypothesis testing will be conducted. Table 8 provides the probability that the objective response rate of each tumor type is claimed clinical meaningful under different true ORR. Table 9 shows the hypothetical ORR estimates and the CI (Clopper-Pearson interval) based on sample size of 20 per tumor type. Due to a small sample size, even an observed response rate as high as 30% (6 out of 20) could be coming from a true signal as low as 14%. A higher observed responses rate such as 8 out of 20 would be more indicative of a true response rate above 20%.

Table 8 Probability That ORR is Claimed as Clinical Interest With 20 Participants in Each Tumor Type of Each Arm

Tumor Type	ORR as clinical meaningful	True ORR	Minimum Responses that ORR is claimed as clinical meaningful	Probability that ORR is claimed as clinical meaningful
CRC	16%	1%	2	1%
		16%	2	77%
NSCLC, Prostate	20%	5%	3	7%
		20%	3	76%

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

Hypothetical number of responses (CR or PR)	ORR	90% CI of ORR	80% CI of ORR
2	10%	(1.8%, 28.3%)	(2.7%, 24.5%)
3	15%	(4.2%, 34.4%)	(5.6%, 30.4%)
4	20%	(7.1%, 40.1%)	(9.0%, 36.1%)
5	25%	(10.4%, 45.6%)	(12.7%, 41.5%)
6	30%	(14.0%, 50.8%)	(16.6%, 46.7%)
7	35%	(17.7%, 55.8%)	(20.7%, 51.8%)
8	40%	(21.7%, 60.6%)	(24.9%, 56.7%)

10.10 Subgroup Analyses

Efficacy endpoints will be analyzed by arm for each tumor type. Additional subgroup analyses (e.g., by age, gender, and race) may be conducted as needed and will be documented in the sSAP.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

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

11. References

[Acharyya S, Oskarsson T, Vanharanta S, Malladi S, Kim J 2012]	Acharyya S, Oskarsson T, Vanharanta S, Malladi S, Kim J, Morris PG, et al. A CXCL1 paracrine network links cancer chemoresistance and metastasis. Cell. 2012 Jul 6;150(1):165-78.	04TLN5
[Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. 2015]	Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. Regulation of tumor metastasis by myeloid-derived suppressor cells. Annu Rev Med. 2015;66:97-110.	04TLNB
[David JM, Dominguez C, Hamilton DH, Palena C. 2016]	David JM, Dominguez C, Hamilton DH, Palena C. The IL-8/IL-8R Axis: A Double Agent in Tumor Immune Resistance. Vaccines (Basel). 2016 Jun 24;4(3).	04TLNF
[Gentles, A. J., et al 2015]	Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nat Med. 2015 Aug;21(8):938-945.	04TR0W

[Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, Morse E 2014]	Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, Morse E, et al. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. Sci Transl Med. 2014 May 21;6(237):237ra67.	04TLNN
[Kumar V, Patel S, Tcyganov E, Gabrilovich DI. 2016]	Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. Trends Immunol. 2016 Mar;37(3):208-220.	04TLNX
[Li, L., et al 2015]	Li L, Xu L, Yan J, Zhen ZJ, Ji Y, Liu CQ, et al. CXCR2 - CXCL1 axis is correlated with neutrophil infiltration and predicts a poor prognosis in hepatocellular carcinoma. J Exp Clin Cancer Res. 2015 Oct 26;34:129.	04TR2B
[Lu X, Horner JW, Paul E, Shang X, Troncoso P, Deng P 2017]	Lu X, Horner JW, Paul E, Shang X, Troncoso P, Deng P, et al. Effective combinatorial immunotherapy for castration-resistant prostate cancer. Nature. 2017 Mar 30;543(7647):728-732.	04TLP3
[Saintigny, P., et al 2013]	Saintigny P, Massarelli E, Lin S, Ahn YH, Chen Y, Goswami S, et al. CXCR2 expression in tumor cells is a poor prognostic factor and promotes invasion and metastasis in lung adenocarcinoma. Cancer Res. 2013 Jan 15;73(2):571-82.	04TR2N
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e152.	04P9RV
[Steele CW, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R 2016]	Steele CW, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R, Rishi L. CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. Cancer Cell. 2016 Jun 13;29(6):832-845.	04TLPZ

[Theivanthiran B, DeVito NC 2017]	Theivanthiran B, DeVito NC, et al. A HSP-TLR-Wnt5a Paracrine Signaling Axis Drives CXCR2 Ligand Recruitment of Myeloid-derived Suppressor Cells and Represents a Novel Adaptive Resistance Mechanism to Anti-PD-1 Antibody Therapy. In: Society for Immunotherapy of Cancer 2017 Abstracts; 8-12 November 2017; Baltimore, Maryland. 2017. P385.	04TLQ2
[Wang G, Lu X, Dey P, Deng P, Wu CC, Jiang S 2016]	Wang G, Lu X, Dey P, Deng P, Wu CC, Jiang S, et al. Targeting YAP-Dependent MDSC Infiltration Impairs Tumor Progression. Cancer Discov. 2016 Jan;6(1):80-95.	04TLQ0

12. Appendices

12.1 Appendix 1: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, 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 participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck 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 which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

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 Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. 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 of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. 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. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck 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. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck 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

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

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck 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.

Merck does not pay for participant referrals. However, Merck 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 Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/IEC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck 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 including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

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.

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 which 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.

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 institutional review board, ethics review committee (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.

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 in order to verify worksheet/case 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/case report form 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.

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.

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.

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 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.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: 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 Merck Code of Conduct for Clinical Trials.

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

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

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

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

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 regulatory authority as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/case report forms.

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.

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.

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.

12.2 Appendix 2: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 9.9 – Future Biomedical Research Sample Collection 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.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the Future Biomedical Research sub-study.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent

forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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.

5. 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 sub-study. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. Questions

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

13. References

1. National Cancer Institute: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; Available from: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal 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 one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in Section 6.1:

- 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 woman of childbearing potential who is not currently pregnant.
    - The following are not acceptable methods of contraception:
        - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).
        - Male condom with cap, diaphragm, or sponge with spermicide.
        - Male and female condoms 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 use a highly effective method of contraception consistently and correctly as described in Table 10 during the protocol-defined time frame in Section 6.1.

Table 10 Highly Effective Contraception Methods

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

Pregnancy Testing

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

A urine pregnancy test is to be obtained within 72 hours prior to first dose.

If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

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

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • 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 treatment. • NOTE: for purposes of AE definition, study treatment (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 treatment 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 treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment 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). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 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 9.3.5 for protocol specific exceptions

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

A 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 a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient'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) which 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 one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

- In addition to the above criteria, adverse events 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.

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 Adverse Event case report forms/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 adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event 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 adverse event 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 adverse event:
    - **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 one 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 one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH 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 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment 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 one 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 adverse event 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 adverse event 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.

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 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection 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 electronic data collection 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 Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

- If the electronic data collection 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 Trial File Binder (or equivalent).

12.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.0 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 11 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	RBC Indices: • Mean Corpuscular Volume (MCV) • Mean Corpuscular Hemoglobin (MCH) • %Reticulocytes		White Blood Cell (WBC) Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Red Blood Cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Chemistry	Sodium	Potassium	Chloride	Phosphorous
	Calcium	Glucose	Bicarbonate / Carbon dioxide (CO_2)[1]	Albumin
	Total Protein	Blood Urea Nitrogen (BUN)[2]	Creatinine (and measured or calculated [per institutional standard] creatinine clearance [CrCl], if creatinine is elevated above 1.5 times the upper limit of normal)[3]	Uric Acid
	Alanine Aminotransferase (ALT) / Serum Glutamic-Pyruvic Transaminase (SGPT)	Aspartate Aminotransferase (AST) / Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Alkaline Phosphatase	Total Bilirubin (and direct bilirubin, if total bilirubin is elevated above 1.5 times the upper limit of normal)
Routine Urinalysis	• Specific Gravity • pH, Glucose, Protein, Blood, Ketones by Dipstick • Microscopic Examination (if blood or protein is abnormal)			
Other Screening Tests	• International Normalized Ratio (INR)/Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT) or Partial thromboplastin time (PTT)[4] • Thyroid Function Testing (T4, T3, TSH)[5] • Urine Pregnancy Test[6] • Serum β-Human Chorionic Gonadotropin (β-hCG)[6] • Follicle-Stimulating Hormone (FSH) and Estradiol (as needed in women of non-childbearing potential only)[7] • Serology (human immunodeficiency virus [HIV] Type 1 and Type 2 antibodies; hepatitis B surface antigen [HBsAg]/hepatitis B virus antibody; and hepatitis C virus antibody ribonucleic acid (HCV RNA)/hepatitis C antibody)[8]			

Laboratory Assessments	Parameters
NOTES: 1. If bicarbonate/CO_2 is not done as part of standard of care in your region, these tests do not need to be performed. 2. Blood urea nitrogen is preferred; if not available, urea may be tested. 3. Glomerular filtration rate (GFR) can be used in place of CrCl. 4. Coagulation factors (INR/PT and aPTT or PTT) should be tested as part of screening procedures for all participants. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study. 5. Total T4 is preferred; if not available, free T4 may be tested. Total T3 is preferred; if not available, free T3 may be tested. 6. Women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required. 7. In women <45 years of age, a high FSH in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. 8. Testing is at the discretion of the investigator.	

Investigators must document their review of each laboratory safety report.

12.6 Appendix 6: Abbreviations and Trademarks

Abbreviation/Acronym	Definition
ADA	Anti-drug antibodies
AE	Adverse Event
AJCC	American Joint Committee on Cancer, version 8
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count (Peripheral Blood)
AP	Alkaline phosphatase
aPTT	activated partial thromboplastin time
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve
BICR	Blinded imaging central review
ß-HCG	Beta-human chorionic gonadotrophin
BUN	Blood urea nitrogen
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Observed Plasma Concentration
C_{trough}	Trough Observed Plasma Concentration
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CO_2	Carbon dioxide
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRPC	Castration resistant prostate cancer
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
CXCL	Cysteine-X-Cysteine Ligand
CXCR1/2	Cysteine-X-Cysteine Chemokine Receptors 1 and 2
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
ELRCXC	Chemokines containing the sequence glutamate-leucine-arginine (ELR) immediately preceding the cysteine-x-cysteine (CXC) motif
EMT	Epithelial-mesenchymal transition
EOT	End of treatment
FAS	Full Analysis Set

Abbreviation/Acronym	Definition
FEV	Forced Expiratory Volume
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor (Filgrastim)
GFR	Glomerular filtration rate
GI	Gastrointestinal
GRO-α	Growth Related Oncogene-Alpha
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
iCPD	iRECIST-confirmed progressive disease
iCR	iRECIST-complete response
IHC	Immunohistochemistry
IL-8	Interleukin-8
INR	International normalized ratio
iPR	iRECIST-partial response
irAE	immune-related adverse event
IRB/IEC	Institutional Review Board/Independent Ethics Committee
iRECIST	Modified response evaluation criteria in solid tumor version 1.1 for immune-based therapeutics
iSD	iRECIST-stable disease
IUD	Intrauterine device
iUPD	iRECIST-unconfirmed progressive disease
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive voice-based registration system
IWRS	Interactive web-based registration system
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDSC	Myeloid derived suppressor cell
MK-3475	pembrolizumab
MK-7123	navarixin
MMP-9	Matrix Metallopeptidase 9
MPO	Myeloperoxidase
MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp.
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high

Abbreviation/Acronym	Definition
MSS CRC	Microsatellite stable colorectal cancer
NCI	National Cancer Institute
NSAID	Non-sterioidal anti-inflammatory drug
NSCLC	Non small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBPK	Physiologically based pharmacokinetic
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-(L)1	Programmed death ligand 1
PFS	Progression free survival
PK	Pharmacokinetics
PO	Per os, orally
POC	Proof-of-Concept
PP	Per protocol
PR	Partial response
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once Daily
Q3W	Once every 3 weeks
R_A	Accumulation Ratio
RBC	Red blood cell
RECIST 1.1	Response evaluation criteria in solid tumor version 1.1
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SCH 527123	Navarixin
SAE	Serious adverse event
SD	Stable disease or standard deviation
SoA	Schedule of Activities
sSAP	supplemental Statistical Analysis Plan
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
T1DM	Type 1 diabetes mellitus
TME	Tumor microenvironment
TPS	Tumor Proportion Score
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman of childbearing potential

12.7 Appendix 7: 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 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

Any participant deemed **clinically unstable** should be discontinued from study 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. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥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 non-target 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 non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, 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 – Non-target.

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 initial iUPD 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 non-target 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 non-target 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 (*For those studies in which PFS is the primary endpoint, add the following:* or if RECIST 1.1 PD has not been verified centrally), 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 Section 2 and submitted to the central imaging vendor.

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.
- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target 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 non-target 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].