Official Protocol Title:	A Phase 1 Study of MK 5890 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors
NCT number:	NCT03396445
Document Date:	04-Aug-2022

Title Page

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

Protocol Title: A Phase 1 Study of MK-5890 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors

Protocol Number: 001-06

Compound Number: MK-5890

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s):

IND NUMBER: 136304

EudraCT NUMBER: 2017-004550-41

Approval Date: 04 August 2022

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:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 6	04-AUG-2022	Merck Sharp and & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 5	27-OCT-2021	To update the frequency of hematology and chemistry panel sample collection in participants with TNBC treated in Arm 4.
Amendment 4	15-JUL-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 3	25-JAN-2021	Cohort expansion to evaluate the efficacy and safety of MK-5890 in combination with pembrolizumab and nab-paclitaxel for the treatment of participants with locally recurrent inoperable TNBC cancer not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC whose tumor PD-L1 CPS is less than 10.
Amendment 2	01-JUL 2019	Based on a review of currently available preclinical and clinical data, several expansion cohorts were added to further examine safety and exploratory efficacy of MK-5890 when used as monotherapy and in combination with pembrolizumab in select tumor types. Furthermore, an additional cohort of participants with nonsquamous NSCLC was added to assess the safety and tolerability of MK-5890 in combination with pembrolizumab and standard chemotherapy.
Amendment 1	09-MAR-2018	The protocol was amended to clarify eligibility of participants; infusion time for MK-5890; noncompliance due to drug-related AE(s); and the assessment and management of potential infusion reactions to MK-5890.
Original Protocol	23-OCT-2017	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 06

Overall Rationale for the Amendment:

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

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page 12.1 Appendix 1: Study Governance Considerations, Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity change and update to address.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. SYNOPSIS

Protocol Title:

A Phase 1 Study of MK-5890 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors

Short Title:

A Phase 1 Study of MK-5890 as Monotherapy and in Combination with Pembrolizumab

Objectives/Hypotheses and Endpoints:

In male and female participants with advanced solid tumors who are at least 18 years of age:

Objectives	**Endpoints**
Primary	
• Objective: To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-5890 when used as monotherapy and in combination with pembrolizumab in the dose escalation and confirmation phase and the dose expansion phase	• Number of participants with a dose-limiting toxicity (DLT) • Number of participants with ≥1 adverse event (AE) • Number of participants who discontinue study treatment due to an AE
Secondary	
• Objective: To evaluate the PK of MK-5890 when given by IV infusion as monotherapy, in combination with pembrolizumab, and in combination with pembrolizumab, pemetrexed and carboplatin and in combination with pembrolizumab and nab-paclitaxel, in the dose escalation and confirmation phase and/or the dose expansion phase	• PK parameters including area under the curve (AUC), minimum concentration (C_{min}), and maximum concentration (C_{max})
• Objective: To evaluate the objective response rate (ORR) of MK-5890 when used as monotherapy, in combination with pembrolizumab, in combination with pembrolizumab and nab-paclitaxel in the dose expansion phase	• ORR as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)

Objectives	Endpoints
• Objective: To determine the safety and tolerability of MK-5890 in combination with pembrolizumab, pemetrexed, and carboplatin in participants with nonsquamous NSCLC and to establish maximum tolerated doses (MTDs) of carboplatin and pemetrexed when used in combination with MK-5890 and pembrolizumab	• Number of participants with a DLT • Number of participants with ≥1 AE • Number of participants who discontinue study treatment due to an AE
• Objective: To determine the safety and tolerability of MK-5890 in combination with pembrolizumab and nab-paclitaxel in participants with locally recurrent inoperable TNBC cancer not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC and to establish MTDs of nab-paclitaxel when used in combination with MK-5890 and pembrolizumab	• Number of participants with a DLT • Number of participants with ≥1 AE • Number of participants who discontinue study treatment due to an AE

Overall Design:

Study Phase	Phase 1
Clinical Indication	Dose escalation and confirmation phase: The treatment of participants with advanced solid tumors Dose expansion phase: The treatment of participants with triple-negative breast cancer (TNBC), nonsquamous NSCLC or endometrial cancer
Population	Participants with a histologically or cytologically confirmed advanced/metastatic solid tumor by pathology report who have received or been intolerant to all treatment known to confer clinical benefit. Participants in the expansion phase (Arm 4) have locally recurrent inoperable TNBC not previously treated with chemotherapy and which cannot be treated with curative intent or with not previously treated metastatic TNBC
Study Type	Interventional

Type of Design	Multi-site, multi-arm, dose escalation, dose confirmation, dose expansion study
Type of Control	No treatment control
Study Blinding	Unblinded open-label
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6.0 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 202 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Participants in the dose escalation/dose confirmation phase will be allocated to 1 of 2 treatment arms: • Arm 1: Escalating doses of MK-5890 given once every 3 weeks (Q3W) as monotherapy; or • Arm 2: Escalating doses of MK-5890 in combination with 200 mg pembrolizumab, both given Q3W. Participants in the dose escalation/dose confirmation phase with nonsquamous non-small cell lung cancer (NSCLC) enrolled as part of Amendment 02 will be allocated to: • Arm 3: 30 mg MK-5890 in combination with 200 mg pembrolizumab, 500 mg/m^2 pemetrexed, and AUC 5 mg/mL/min carboplatin, all given Q3W. Participants in the dose expansion phase with TNBC will be allocated to: • Arm 2a: 30 mg MK-5890 in combination with 200 mg pembrolizumab, both given Q3W. • Arm 4: 30 mg MK-5890 in combination with 400 mg pembrolizumab, 100 mg/m^2 nab-paclitaxel. MK-5890 and pembrolizumab given Q6W for 18 cycles. Nab-paclitaxel administered on a 3-week on (Days 1, 8 and 15)/ 1-week off schedule every 28 days.

	Participants in the dose expansion phase with endometrial cancer will be allocated to: • Arm 1a: 30 mg MK-5890 given Q3W as monotherapy; • Arm 2b: 30 mg MK-5890 in combination with 200 mg pembrolizumab, both given Q3W; or • Arm 2c: 30 mg MK-5890 in combination with 400 mg pembrolizumab, both given once every 6 weeks (Q6W).
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent form (ICF) through the final protocol-specified contact. After a screening period of up to 28 days, each participant will be assigned to receive study treatment until disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy, noncompliance with study treatment or procedure requirements, the participant completes study treatment, administrative reasons requiring cessation of treatment, or death. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in Section 9.3. Participants who discontinue study treatment for reasons other than confirmed disease progression will have post-treatment follow-up imaging every 9 weeks for disease status until disease progression, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, or death. After confirmed disease progression, each participant will be contacted by telephone approximately every 12 weeks for survival until participant withdrawal of consent, becoming lost to follow-up, death, 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 8.

2. SCHEDULE OF ACTIVITIES (SOA)

2.1 Schedule of Activities for the Screening & Treatment Periods - Dose Escalation and Confirmation Phase (Arms 1 and 2)

Note: Participants in Arms 1 and 2 of the dose escalation and confirmation phase will follow the SoA in Section 2.7 for the End of Treatment and Post-Treatment Follow-Up Periods.

Study Period	Screening	Treatment Period Cycle = 21 days														Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1							Cycles 2-4						Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	5	8	15	1	2	3	5	8	15	Every 9 weeks	1	
Administrative Procedures																
Informed Consent	X															Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (FBR)	X															
Inclusion/Exclusion Criteria	X															
Participant Identification Card	X															
Demographics and Medical History	X															
Oncology Disease Status and Prior Oncology Treatment History	X															
Concomitant Medication	X	X	X			X	X	X	X			X	X		X	
Clinical Procedures/Assessments																
Physical Examination	X	X[2]						X[2]							X[2]	A full physical examination should be done at screening. Directed physical examinations may be done at the other time points unless a full examination is deemed necessary.
Height	X															
Weight	X	X						X							X	
Vital Signs	X	X	X	X		X	X	X	X	X		X	X		X	To be measured at screening and prior to dosing, and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1 and once daily on Day 2, Day 3, Day 8, and Day 15 of Cycles 1-4. In Cycles ≥5, measured prior to dosing on Day 1 only. Measurements include temperature, pulse, respiratory rate, blood pressure.
ECOG Performance Status	X	X[2]						X[2]							X[2]	Should be performed at screening and prior to dosing on Day 1 of each cycle.
12-Lead Electrocardiogram	X	X[2]						X[2]								Performed at screening and prior to dosing and within 30 minutes after the end of the MK-5890 infusion on Day 1 of Cycles 1-4.

Study Period	Screening	Treatment Period Cycle = 21 days													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1						Cycles 2-4						Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	5	8	15	1	2	3	5	8	15	Every 9 weeks	1	
CCI	CCI															CCI
CCI	CCI															
Adverse Event Monitoring	X	X	X	X		X	X	X	X	X		X	X		X	All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. Continuous AE reporting from the time of treatment allocation.
Tumor Imaging and Response Assessment	X													X	X	At screening and every 9 weeks from the first dose of study treatment.
Survival Status		←													→	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments – LOCAL																
Hematology	X[1]	X[2]	X			X	X	X[2]				X	X		X[2]	To be collected at screening and prior to dosing and 4 hours after the start of the MK-5890 infusion on Day 1 of Cycles 1-4. In Cycle 1, should also be collected once daily on Day 2, Day 8, and Day 15. In Cycles 2-4, should also be collected once daily on Day 8 and Day 15. In Cycles ≥5, to be collected prior to dosing on Day 1 only.
Chemistry Panel	X[1]	X[2]	X			X	X	X[2]				X	X		X[2]	
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)	X[1]															Participants on anticoagulant therapy should be monitored throughout the study.
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[1]	X[2]						X[2]							X[2]	
Thyroid Function Testing (T4, T3, TSH)	X	X[2]						X							X	After Cycle 1, samples are collected every other cycle.
Pregnancy Test (urine or serum β-human chorionic gonadotropin [β-hCG]) - Women of childbearing potential only	X	X[2]														Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly testing should be conducted per local regulations.

Study Period	Screening	Treatment Period Cycle = 21 days													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1						Cycles 2-4						Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	5	8	15	1	2	3	5	8	15	Every 9 weeks	1	
HIV/Hepatitis Screen (at the discretion of the investigator)	X															Per local regulations.
Urinalysis	X[1]															
CCI [redacted]																
Blood for RNA Analyses		X						X							X	To be collected prior to dosing on Day 1 of Cycles 1-5.
Serum for Biomarker Analyses[3]	X	X	X			X		X	X			X			X	To be collected at screening and prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 and once daily on Day 2 and Day 8 of Cycles 1-4. In Cycles ≥5, to be collected prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 only.
Peripheral Blood Mononuclear Cell (PBMC) Collection for Biomarker Analyses		X						X							X	To be collected prior to dosing on Day 1 of Cycles 1-4 and every 4 cycles thereafter. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Immunophenotyping[3]	X	X				X	X	X				X	X		X	To be collected at screening and prior to dosing on Day 1 and once daily on Day 8 and Day 15 of Cycles 1-4. In Cycles ≥5, to be collected prior to dosing on Day 1 only. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Genetic Analyses		X														If there is either a documented law or regulation prohibiting collection of blood for genetic analyses, or if the IRB/IEC does not approve the collection, sampling will not be done at the site. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR only.

Study Period	Screening	Treatment Period Cycle = 21 days													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1						Cycles 2-4							Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	5	8	15	1	2	3	5	8	15	Every 9 weeks	1	
Tumor Tissue Collection	X															Required at screening for all participants. Newly obtained tumor tissue is defined as tissue collected within 90 days before the first dose of study treatment. Archival tumor tissue is defined as tissue collected greater than 90 days before the first dose of study treatment. The actual tumor sample is not required to be at the study site within the 28-day screening period.
Post-Treatment Tumor Biopsy												X				Requested between Day 8 and Day 15 of Cycle 2.
Blood for Receptor Availability Analysis[3]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	To be collected at screening and prior to dosing at the end of the MK-5890 infusion (+10 minutes) and 2 hours after the start of the MK-5890 infusion (+/-10 minutes) on Day 1, and once daily on Day 2, Day 3, Day 5, Day 8, and Day 15 of Cycles 1-4. In addition, samples should be collected prior to dosing on Day 1 of Cycles 5 and 6.
Serum for Soluble Receptor Analysis[3]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

1. Laboratory test at screening are to be performed within 7 days before the first dose of study treatment.
2. Procedure/sample collection may be performed up to 72 hours before the first dose of study treatment. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point.
3. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.

2.2 Schedule of Activities for the Screening & Treatment Periods – Dose Escalation and Confirmation Phase (Arm 3: 30 mg MK-5890 + 200 mg Pembrolizumab + 500 mg/m^2 Pemetrexed + AUC 5 mg/mL/min Carboplatin, all Q3W in Participants With Nonsquamous NSCLC)

Note: Participants in Arm 3 of the dose escalation and confirmation phase will follow the SoA in Section 2.7 for the End of Treatment and Post-Treatment Follow-Up Periods.

Study Period	Screening	Treatment Period Cycle = 21 days												Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4						Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	2	3	8	15	Every 9 weeks	1	
Administrative Procedures														
Informed Consent	X													Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (FBR)	X													
Inclusion/Exclusion Criteria	X													
Participant Identification Card	X													
Demographics and Medical History	X													
Oncology Disease Status and Prior Oncology Treatment History	X													
Concomitant Medication	X	X	X		X	X	X	X		X	X		X	
Clinical Procedures/Assessments														
Physical Examination	X	X[2]					X[2]						X[2]	A full physical examination should be done at screening. Directed physical examinations may be done at the other time points unless a full examination is deemed necessary.
Height	X													
Weight	X	X					X						X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X		X	To be measured at screening and prior to dosing and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1, and once daily on Day 2, Day 3, Day 8, and Day 15 of Cycles 1-4. In Cycles ≥5, measured prior to dosing on Day 1 only. Measurements include temperature, pulse, respiratory rate, blood pressure.
ECOG Performance Status	X	X[2]					X[2]						X[2]	Should be performed at screening and prior to dosing on Day 1 of each cycle.
12-Lead Electrocardiogram	X	X[2]					X[2]							Performed at screening and prior to dosing and within 30 minutes after the end of the MK-5890 infusion on Day 1 of Cycles 1-4.

Study Period	Screening	Treatment Period Cycle = 21 days											
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4						Cycles ≥5
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	2	3	8	15	Every 9 weeks	1
CCI [redacted]													
Pemetrexed Drug Administration		X					X						X
Carboplatin Drug Administration		X					X						
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X		X
Tumor Imaging and Response Assessment	X											X	X
Survival Status		←											→
Laboratory Procedures/Assessments – LOCAL													
Hematology	X[1]	X[2]	X		X	X	X[2]			X	X		X[2]
Chemistry Panel	X[1]	X[2]	X		X	X	X[2]			X	X		X[2]
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)	X[1]												
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[1]	X[2]					X[2]						X[2]
Creatinine Clearance (CrCl) Calculation	X[1]	X[2]					X[2]						

Notes
CCI [redacted]
All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. Continuous AE reporting from the time of treatment allocation.
At screening and every 9 weeks from the first dose of study treatment.
Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
To be collected at screening and prior to dosing and 4 hours after the start of the MK-5890 infusion on Day 1 of Cycles 1-4. In Cycle 1, should also be collected once daily on Day 2, Day 8, and Day 15. In Cycles 2-4, should also be collected once daily on Day 8 and Day 15. In Cycles ≥5, to be collected prior to dosing on Day 1 only.
Participants on anticoagulant therapy should be monitored throughout the study.

Study Period	Screening	Treatment Period Cycle = 21 days											Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4					Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	2	3	8	15	Every 9 weeks	1	
Thyroid Function Testing (T4, T3, TSH)	X	X[2]					X						X	After Cycle 1, samples are collected every other cycle.
Pregnancy Test (urine or serum β-human chorionic gonadotropin [β-hCG]) - Women of childbearing potential only	X	X[2]												Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly testing should be conducted per local regulations.
HIV/Hepatitis Screen (at the discretion of the investigator)	X													Per local regulations.
Urinalysis	X[1]													
Laboratory Procedures/Assessments – CENTRAL														
CCI [redacted]														
Pharmacokinetic Sampling for Pemetrexed[3]		X	X				X	X					X	Samples for pemetrexed PK testing should be collected prior to dosing and at the end of the pemetrexed infusion (+10 minutes) on Day 1 and once on Day 2 of Cycles 1 and 2 and prior to dosing and at the end of the pemetrexed infusion (+10 minutes) on Day 1 of Cycle 8.
Pharmacokinetic Sampling for Carboplatin[3]		X	X				X	X						Samples for carboplatin PK testing should be collected prior to dosing and at the end of the carboplatin infusion (+10 minutes) on Day 1 and once on Day 2 of Cycles 1 and 2.

Study Period	Screening	Treatment Period Cycle = 21 days											Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4					Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	2	3	8	15	Every 9 weeks	1	
Blood for circulating tumor DNA (ctDNA) Analysis		X					X						X	To be collected prior to dosing on Day 1 of Cycles 1-5.
Blood for RNA Analyses		X					X						X	
Serum for Biomarker Analyses[3]	X	X	X		X		X						X	To be collected at screening and prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 and once daily on Day 2 and Day 8 of Cycle 1. In Cycles 2-8, to be collected prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 only.
Peripheral Blood Mononuclear Cell (PBMC) Collection for Biomarker Analyses		X					X						X	To be collected prior to dosing on Day 1 of Cycles 1-4 and every 4 cycles thereafter. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Immunophenotyping[3]	X	X			X	X	X						X	To be collected at screening and prior to dosing on Day 1, and once daily on Day 8 and Day 15 of Cycle 1. In Cycles 2-8, to be collected prior to dosing on Day 1 only. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Genetic Analyses		X												If there is either a documented law or regulation prohibiting collection of blood for genetic analyses, or if the IRB/IEC does not approve the collection, sampling will not be done at the site. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR only.
Tumor Tissue Collection	X													Required at screening for all participants. Newly obtained tumor tissue is defined as tissue collected within 90 days before the first dose of study treatment. Archival tumor tissue is defined as tissue collected greater than 90 days before the first dose of study treatment. The actual tumor sample is not
CCI														CCI
Serum for Soluble Receptor Analysis[3]	X	X	X	X	X	X	X						X	

1. Laboratory test at screening are to be performed within 7 days before the first dose of study treatment.
2. Procedure/sample collection may be performed up to 72 hours before the first dose of study treatment. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point.
3. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.

2.3 Schedule of Activities for the Screening & Treatment Periods - Dose Expansion Phase (Arm 1a: 30 mg MK-5890 Q3W as Monotherapy in Participants With Endometrial Cancer)

Note: Participants in Arm 1a of the dose expansion phase will follow the SoA in Section 2.7 for the End of Treatment and Post-Treatment Follow-Up Periods.

Study Period	Screening	Treatment Period Cycle = 21 days										Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4				Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	8	15	Every 9 weeks	1	
Administrative Procedures												
Informed Consent	X											Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (FBR)	X											
Inclusion/Exclusion Criteria	X											
Participant Identification Card	X											
Demographics and Medical History	X											
Oncology Disease Status and Prior Oncology Treatment History	X											
Concomitant Medication	X	X	X		X	X	X	X	X		X	
Clinical Procedures/Assessments												
Physical Examination	X	X[2]					X[2]				X[2]	A full physical examination should be done at screening. Directed physical examinations may be done at the other time points unless a full examination is deemed necessary.
Height	X											
Weight	X	X					X				X	
Vital Signs	X	X	X	X	X	X	X	X	X		X	To be measured at screening and prior to dosing and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1, and once daily on Day 2, Day 3, Day 8, and Day 15 of Cycle 1. In Cycles 2-4, measured prior to dosing and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1 and once daily on Day 8 and Day 15. In Cycles ≥5, measured prior to dosing on Day 1 only. Measurements include temperature, pulse, respiratory rate, blood pressure.
ECOG Performance Status	X	X[2]					X[2]				X[2]	Should be performed at screening and prior to dosing on Day 1 of each cycle.
12-Lead Electrocardiogram	X											

Study Period	Screening	Treatment Period Cycle = 21 days										Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4				Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	8	15	Every 9 weeks	1	
CCI [redacted]												
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X		X	All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. Continuous AE reporting from the time of treatment allocation.
Tumor Imaging and Response Assessment	X									X	X	At screening and every 9 weeks from the first dose of study treatment.
Survival Status		←									→	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments – LOCAL												
Hematology	X[1]	X[2]	X		X	X	X[2]	X	X		X[2]	To be collected at screening and prior to dosing and 4 hours after the start of the MK-5890 infusion on Day 1 of Cycles 1-4. In Cycle 1, should also be collected once daily on Day 2, Day 8, and Day 15. In Cycles 2-4, should also be collected once daily on Day 8 and Day 15. In Cycles ≥5, to be collected prior to dosing on Day 1 only.
Chemistry Panel	X[1]	X[2]	X		X	X	X[2]	X	X		X[2]	
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)	X[1]											Participants on anticoagulant therapy should be monitored throughout the study.
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[1]	X[2]					X[2]				X[2]	
Thyroid Function Testing (T4, T3, TSH)	X	X[2]					X				X	After Cycle 1, samples are collected every other cycle.
Pregnancy Test (urine or serum β-human chorionic gonadotropin [β-hCG]) - Women of childbearing potential only	X	X[2]										Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly testing should be conducted per local regulations.
HIV/Hepatitis Screen (at the discretion of the investigator)	X											Per local regulations.
Urinalysis	X[1]											

Study Period	Screening	Treatment Period Cycle = 21 days										Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4				Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	8	15	Every 9 weeks	1	
Laboratory Procedures/Assessments – CENTRAL												
CCI [redacted]												
Blood for circulating tumor DNA (ctDNA) Analysis		X					X				X	To be collected prior to dosing on Day 1 of Cycles 1-5.
Blood for RNA Analyses		X					X				X	
Serum for Biomarker Analyses[3]	X	X	X		X		X				X	To be collected at screening and prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 and once daily on Day 2 and Day 8 of Cycle 1. In Cycles ≥2, to be collected prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 only.
Peripheral Blood Mononuclear Cell (PBMC) Collection for Biomarker Analyses		X					X				X	To be collected prior to dosing on Day 1 of Cycles 1-4 and every 4 cycles thereafter. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Immunophenotyping[3]	X	X			X	X	X				X	To be collected at screening and prior to dosing on Day 1 and once daily on Day 8 and Day 15 of Cycle 1. In Cycles ≥2, to be collected prior to dosing on Day 1 only. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Genetic Analyses		X										If there is either a documented law or regulation prohibiting collection of blood for genetic analyses, or if the IRB/IEC does not approve the collection, sampling will not be done at the site. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR only.
Tumor Tissue Collection	X											Required at screening for all participants. Newly obtained tumor tissue is defined as tissue collected within 90 days before the first dose of study treatment. Archival tumor tissue is defined as tissue collected greater than 90 days before the first dose of study treatment. The actual tumor sample is not required to be at the study site within the 28-day screening period.
Post-Treatment Tumor Biopsy								X				Requested between Day 8 and Day 15 of Cycle 2.

Study Period	Screening	Treatment Period Cycle = 21 days									Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4				Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	8	15	Every 9 weeks	1	
CCI												CCI
Serum for Soluble Receptor Analysis[3]	X	X	X	X	X	X	X				X	

1. Laboratory test at screening are to be performed within 7 days before the first dose of study treatment.
2. Procedure/sample collection may be performed up to 72 hours before the first dose of study treatment. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point.
3. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.

2.4 Schedule of Activities for the Screening & Treatment Periods - Dose Expansion Phase (Arm 2a: 30 mg MK-5890 + 200 mg Pembrolizumab, Both Q3W in Participants With TNBC AND Arm 2b: 30 mg MK-5890 + 200 mg Pembrolizumab, Both Q3W in Participants With Endometrial Cancer)

Note: Participants in Arms 2a and 2b of the dose expansion phase will follow the SoA in Section 2.7 for the End of Treatment and Post-Treatment Follow-Up Periods.

Study Period	Screening	Treatment Period Cycle = 21 days										Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4				Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	8	15	Every 9 weeks	1	
Administrative Procedures												
Informed Consent	X											Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (FBR)	X											
Inclusion/Exclusion Criteria	X											
Participant Identification Card	X											
Demographics and Medical History	X											
Oncology Disease Status and Prior Oncology Treatment History	X											
Concomitant Medication	X	X	X		X	X	X	X	X		X	
Clinical Procedures/Assessments												
Physical Examination	X	X[2]					X[2]				X[2]	A full physical examination should be done at screening. Directed physical examinations may be done at the other time points unless a full examination is deemed necessary.
Height	X											
Weight	X	X					X				X	
Vital Signs	X	X	X	X	X	X	X	X	X		X	To be measured at screening and prior to dosing and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1, and once daily on Day 2, Day 3, Day 8, and Day 15 of Cycle 1. In Cycles 2-4, measured prior to dosing and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1, and once daily on Day 8 and Day 15. In Cycles ≥5, measured prior to dosing on Day 1 only. Measurements include temperature, pulse, respiratory rate, blood pressure.
ECOG Performance Status	X	X[2]					X[2]				X[2]	Should be performed at screening and prior to dosing on Day 1 of each cycle.
12-Lead Electrocardiogram	X											

Study Period	Screening	Treatment Period Cycle = 21 days										Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4				Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	8	15	Every 9 weeks	1	
CCI [redacted]												
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X		X	All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. Continuous AE reporting from the time of treatment allocation.
Tumor Imaging and Response Assessment	X									X	X	At screening and every 9 weeks from the first dose of study treatment.
Survival Status		←									→	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments – LOCAL												
Hematology	X[1]	X[2]	X		X	X	X[2]	X	X		X[2]	To be collected at screening and prior to dosing and 4 hours after the start of the MK-5890 infusion on Day 1 of Cycles 1-4. In Cycle 1, should also be collected once daily on Day 2, Day 8, and Day 15. In Cycles 2-4, should also be collected once daily on Day 8 and Day 15. In Cycles ≥5, to be collected prior to dosing on Day 1 only.
Chemistry Panel	X[1]	X[2]	X		X	X	X[2]	X	X		X[2]	
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)	X[1]											Participants on anticoagulant therapy should be monitored throughout the study.
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[1]	X[2]					X[2]				X[2]	
Thyroid Function Testing (T4, T3, TSH)	X	X[2]					X				X	After Cycle 1, samples are collected every other cycle.
Pregnancy Test (urine or serum β-human chorionic gonadotropin [β-hCG]) - Women of childbearing potential only	X	X[2]										Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly testing should be conducted per local regulations.
HIV/Hepatitis Screen (at the discretion of the investigator)	X											Per local regulations.
Urinalysis	X[1]											

Study Period	Screening	Treatment Period Cycle = 21 days										Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4				Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	8	15	Every 9 weeks	1	
Laboratory Procedures/Assessments – CENTRAL												
CCI [redacted]												
Blood for circulating tumor DNA (ctDNA) Analysis		X					X				X	To be collected prior to dosing on Day 1 of Cycles 1-5.
Blood for RNA Analyses		X					X				X	
Serum for Biomarker Analyses[3]	X	X	X		X		X				X	To be collected at screening and prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 and once daily on Day 2 and Day 8 of Cycle 1. In Cycles 2-8, to be collected prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 only.
Peripheral Blood Mononuclear Cell (PBMC) Collection for Biomarker Analyses		X					X				X	To be collected prior to dosing on Day 1 of Cycles 1-4 and every 4 cycles thereafter. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Immunophenotyping[3]	X	X			X	X	X				X	To be collected at screening and prior to dosing on Day 1 and once daily on Day 8 and Day 15 of Cycle 1. In Cycles 2-8, to be collected prior to dosing on Day 1 only. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.

Study Period	Screening	Treatment Period Cycle = 21 days										Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1					Cycles 2-4				Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	1	8	15	Every 9 weeks	1	
Blood for Genetic Analyses		X										If there is either a documented law or regulation prohibiting collection of blood for genetic analyses, or if the IRB/IEC does not approve the collection, sampling will not be done at the site. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR only.
Tumor Tissue Collection	X											Required at screening for all participants. Newly obtained tumor tissue is defined as tissue collected within 90 days before the first dose of study treatment. Archival tumor tissue is defined as tissue collected greater than 90 days before the first dose of study treatment. The actual tumor sample is not required to be at the study site within the 28-day screening period.
Post-Treatment Tumor Biopsy								X				Requested between Day 8 and Day 15 of Cycle 2.
CCI												CCI
Serum for Soluble Receptor Analysis[3]	X	X	X	X	X	X	X				X	

1. Laboratory test at screening are to be performed within 7 days before the first dose of study treatment.
2. Procedure/sample collection may be performed up to 72 hours before the first dose of study treatment. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point.
3. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.

2.5 Schedule of Activities for the Screening & Treatment Periods - Dose Expansion Phase (Arm 2c: 30 mg MK-5890 + 400 mg Pembrolizumab, Both Q6W in Participants With Endometrial Cancer)

Note: Participants in Arm 2c of the dose expansion phase will follow the SoA in Section 2.7 for the End of Treatment and Post-Treatment Follow-Up Periods.

Study Period	Screening	Treatment Period Cycle = 42 days														Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2-4					Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	Every 9 weeks	1	
Administrative Procedures																	
Informed Consent	X																Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (FBR)	X																
Inclusion/Exclusion Criteria	X																
Participant Identification Card	X																
Demographics and Medical History	X																
Oncology Disease Status and Prior Oncology Treatment History	X																
Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X	X	X		X	
Clinical Procedures/Assessments																	
Physical Examination	X	X[2]					X	X	X	X[2]				X		X[2]	A full physical examination should be done at screening. Directed physical examinations may be done at the other time points unless a full examination is deemed necessary.
Height	X																
Weight	X	X					X	X	X	X				X		X	

Study Period	Screening	Treatment Period Cycle = 42 days															Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2-4						Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	Every 9 weeks	1	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	To be measured at screening and prior to dosing and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1, and once daily on Day 2, Day 3, Day 8, Day 15, Day 22, Day 29, and Day 36 of Cycle 1. In Cycles 2-4, measured prior to dosing, and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1, and once daily on Day 2, Day 8, Day 15, and Day 22. In Cycles ≥5, measured prior to dosing on Day 1 only. Measurements include temperature, pulse, respiratory rate, blood pressure.
ECOG Performance Status	X	X[2]					X			X[2]				X		X[2]	Should be performed at screening and prior to dosing on Day 1 and once on Day 22 of Cycles 1-4. In Cycles ≥5, performed prior to dosing on Day 1 only.
12-Lead Electrocardiogram	X																
CCI [redacted]																	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. Continuous AE reporting from the time of treatment allocation.
Tumor Imaging and Response Assessment	X														X	X	At screening and every 9 weeks from the first dose of study treatment.
Survival Status		←														→	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments – LOCAL																	
Hematology	X[1]	X[2]	X		X	X	X			X[2]		X	X	X		X[2]	To be collected at screening and prior to dosing and 4 hours after the start of the MK-5890 infusion on Day 1 of Cycles 1-4. In Cycle 1, should also be collected once daily on Day 2, Day 8, Day 15, and Day 22. In Cycles 2-4, should also be collected once daily on Day 8, Day 15, and Day 22. In Cycles ≥5, to be collected prior to dosing on Day 1 only. Additional sampling should be performed as clinically indicated.
Chemistry Panel	X[1]	X[2]	X		X	X	X			X[2]		X	X	X		X[2]	

Study Period	Screening	Treatment Period Cycle = 42 days														Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2-4						Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	Every 9 weeks	1	
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)	X[1]																Participants on anticoagulant therapy should be monitored throughout the study.
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[1]	X[2]								X[2]						X[2]	
Thyroid Function Testing (T4, T3, TSH)	X	X[2]								X						X	After Cycle 1, samples are collected every other cycle.
Pregnancy Test (urine or serum β-human chorionic gonadotropin [β-hCG]) - Women of childbearing potential only	X	X[2]															Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly testing should be conducted per local regulations.
HIV/Hepatitis Screen (at the discretion of the investigator)	X																Per local regulations.
Urinalysis	X[1]																
Laboratory Procedures/Assessments – CENTRAL																	
CCI [redacted]																	

Study Period	Screening	Treatment Period Cycle = 42 days														Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2-4						Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	Every 9 weeks	1	
CCI [redacted]																	
Blood for circulating tumor DNA (ctDNA) Analysis		X								X						X	To be collected prior to dosing on Day 1 of Cycles 1-5.
Blood for RNA Analyses		X								X						X	
Serum for Biomarker Analyses[3]	X	X	X		X					X							To be collected at screening and prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 and once daily on Day 2 and Day 8 of Cycle 1. In Cycles 2-4, to be collected prior to dosing and 2 hours after the start of the MK-5890 infusion on Day 1 only.
Peripheral Blood Mononuclear Cell (PBMC) Collection for Biomarker Analyses		X								X						X	To be collected prior to dosing on Day 1 of Cycles 1-4 and every 2 cycles thereafter. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Immunophenotyping[3]	X	X			X	X	X			X							To be collected at screening and prior to dosing on Day 1 and once daily on Day 8, Day 15, and Day 22 of Cycle 1. In Cycles 2-4, to be collected prior to dosing on Day 1 only. An additional sample will be collected to coincide with the optional post-treatment tumor biopsy.
Blood for Genetic Analyses		X															If there is either a documented law or regulation prohibiting collection of blood for genetic analyses, or if the IRB/IEC does not approve the collection, sampling will not be done at the site. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR only.
Tumor Tissue Collection	X																Required at screening for all participants. Newly obtained tumor tissue is defined as tissue collected within 90 days before the first dose of study treatment. Archival tumor tissue is defined as tissue collected greater than 90 days before the first dose of study treatment. The actual tumor sample is not required to be at the study site within the 28-day screening period.
Post-Treatment Tumor Biopsy												X					Requested between Day 8 and Day 15 of Cycle 2.

Study Period	Screening	Treatment Period Cycle = 42 days														Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2-4					Cycles ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	Every 9 weeks	1	
CCI																	CCI
Serum for Soluble Receptor Analysis[3]	X	X	X	X	X	X	X			X				X			

1. Laboratory test at screening are to be performed within 7 days before the first dose of study treatment.
2. Procedure/sample collection may be performed up to 72 hours before the first dose of study treatment. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point.
3. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.

2.6 Schedule of Activities for the Screening & Treatment Periods - Cohort Expansion Phase (Arm 4: MK-5890 + Pembrolizumab, Both Q6W, Plus nab-Paclitaxel in Participants With Locally Recurrent Inoperable TNBC not Previously Treated With Chemotherapy and Which Cannot be Treated With Curative Intent or With not Previously Treated Metastatic TNBC Whose Tumor PD-L1 CPS is Less Than 10)

Note: Participants in Arm 4 of the dose expansion phase will follow the SoA in Section 2.7 for the End of Treatment and Post-Treatment Follow-Up Periods.

Study Period	Screening	Treatment Period Cycle = 42 days																													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2							Cycle 3							Cycle 4							Every 9 weeks	Cycle ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36		1/8/15/ 22/29/36	
Administrative Procedures																																	
Informed Consent	X																																Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (FBR)	X																																
Inclusion/Exclusion Criteria	X																																
Participant Identification Card	X																																
Demographics and Medical History	X																																
Oncology Disease Status and Prior Oncology Treatment History	X																																

Study Period	Screening	Treatment Period Cycle = 42 days																													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2							Cycle 3							Cycle 4							Every 9 weeks	Cycle ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36		1/8/15/ 22/29/36	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Clinical Procedures/Assessments																																	
Physical Examination	X	X[2]			X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X		X	A full physical examination should be done at screening. Directed physical examinations should be done weekly thereafter as of Cycle 1, Day 1 unless a full examination is deemed necessary.
Height	X																																
Weight	X	X								X							X							X								X	Measured at screening and prior to dosing on Day 1 of each cycle.
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	Measured at screening and prior to dosing and 2 hours, 4 hours, and 6 hours after the start of MK-5890 infusion on Day 1, and once daily on Day 2, Day 3, Day 8, Day 15, Day 22, Day 29, and Day 36 of Cycle 1. In Cycles 2-4, measured prior to dosing, and 2 hours, 4 hours, and 6 hours after the start of MK-5890 infusion on Day 1, and once daily on Day 2, Day 8, Day 15, Day 22, Day 29, and Day 36. In Cycles ≥5, measured prior to dosing on Day 1 only. [a] Includes temperature, pulse, respiratory rate, blood pressure.
ECOG Performance Status	X	X[2]					X			X				X			X				X			X				X				X	To be performed at screening and prior to dosing on Day 1 and once on Day 22 of Cycles 1-4. In Cycles ≥5, performed prior to dosing on Day 1 only.
12-Lead Electrocardiogram	X																																

Study Period	Screening	Treatment Period Cycle = 42 days																													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1							Cycles 2							Cycle 3							Cycle 4							Every 9	Cycle ≥5	
																														1/8/15/		
CCI [redacted]																																
Nab-paclitaxel Drug Administration		X			X	X		X	X	X			X	X	X		X		X	X		X	X	X		X	X	X			X[b]	Nab-paclitaxel will be given on a 3-week on/1-week off schedule every 28 days. Participants should receive premedication for nab-paclitaxel per approved product labels. [b] In odd-numbered cycles ≥5 (i.e., 5, 7, 9, etc.), Nab-paclitaxel will be administered on Days 1, 8, 15, 29, and 36. In even-numbered cycles ≥5 (i.e., 6, 8, 10, etc.), Nab-paclitaxel will be administered on Days 1, 15, 22, and 29.

Study Period	Screening	Treatment Period Cycle = 42 days																													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2							Cycle 3							Cycle 4							Every 9 weeks	Cycle ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36		1/8/15/ 22/29/36	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	All adverse events occurring after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. Continuous AE reporting from the time of treatment allocation.
Tumor Imaging and Response Assessment	X																														X	X	At screening and every 9 weeks from the first dose of study treatment.
Survival Status		←																												→			Upon Sponsor request, participants may be contacted for survival status at any time during course of study.

Study Period	Screening	Treatment Period Cycle = 42 days																													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2							Cycle 3							Cycle 4							Every 9 weeks	Cycle ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36		1/8/15/ 22/29/36	
Laboratory Procedures/Assessments – LOCAL																																	
Hematology	X[1]	X[2]	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X		X	Collected at screening and prior to dosing and 4 hours after the start of the MK-5890 infusion on Day 1 and once daily on Day 2 (Cycle 1 only), Day 8, Day 15, Day 22, Day 29, and Day 36 of Cycles 1-4. In odd-numbered cycles ≥5 (i.e., 5, 7, 9, etc.), collected once daily on Days 1, 8, 15, 29, and 36. In even-numbered cycles ≥5 (i.e., 6, 8, 10, etc.), collected once daily on Days 1, 15, 22, and 29. Additional sampling should be performed as clinically indicated.
Chemistry Panel	X[1]	X[2]	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X		X	
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)	X[1]																																Participants on anticoagulant therapy should be monitored throughout the study.
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[1]	X[2]								X							X							X								X	Collected at screening and prior to dosing on Day 1 of each cycle.
Thyroid Function Testing (T4, T3, TSH)	X	X[2]															X																X	After Cycle 1, samples are collected prior to dosing on Day 1 of every other cycle.

Study Period	Screening	Treatment Period Cycle = 42 days																												Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2							Cycle 3							Cycle 4							Every 9 weeks	Cycle ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36		1/8/15/ 22/29/36	
Pregnancy Test (urine or serum β-human chorionic gonadotropin [β-hCG]) - Women of childbearing potential only	X	X[2]																															Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly testing should be conducted per local regulations.
HIV/Hepatitis Screen (at the discretion of the investigator)	X																																Per local regulations.
Urinalysis	X[1]																																
Laboratory Procedures/Assessments – CENTRAL																																	
CCI [redacted]																																	

Study Period	Screening	Treatment Period Cycle = 42 days																												Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2							Cycle 3							Cycle 4							Every 9 weeks	Cycle ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36		1/8/15/ 22/29/36	
CCI [redacted]																																	
Blood for circulating tumor DNA (ctDNA) Analysis		X					X			X				X										X								X	To be collected predose on Day 1 of Cycles 1, 2, 4, 7, 10, 13, 16 and on Day 22 of Cycles 1, 2, 5, 8, 11, 14, and 17.
Blood for RNA Analyses		X								X							X							X									To be collected prior to dosing on Day 1 of Cycles 1-4.
Serum for Biomarker Analyses[3]	X	X	X							X							X							X								X	To be collected at screening, prior to dosing and 2 hours after the start of the MK-5890 infusion (± 10 minutes) on Day 1, and once on Day 2 of Cycle 1, and prior to dosing and 2 hours after the start of the MK-5890 infusion (± 10 minutes) on Day 1 of Cycles 2-6.

Study Period	Screening	Treatment Period Cycle = 42 days																													Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2							Cycle 3							Cycle 4							Every 9 weeks	Cycle ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36		1/8/15/ 22/29/36	
Peripheral Blood Mononuclear Cell (PBMC) Collection for Biomarker Analyses		X								X							X							X									To be collected prior to dosing on Day 1 of Cycles 1-4.
Blood for Immunophenotyping[3]	X	X					X			X				X			X				X			X									To be collected at screening prior to dosing on Day 1 of Cycles 1-4, and on Day 22 of Cycles 1-3.
Blood for Genetic Analyses		X																															To be collected predose. If there is either a documented law or regulation prohibiting collection of blood for genetic analyses, or if the IRB/IEC does not approve the collection, sampling will not be done at the site. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR only.
Tumor Tissue Collection	X																																Required at screening for all participants. Newly obtained tumor tissue is defined as tissue collected within 90 days before the first dose of study treatment. Archival tumor tissue is defined as tissue collected more than 90 days before the first dose of study treatment. The actual tumor sample is not required to be at the study site within the 28-day screening period.
PD-L1 testing of tumor sample for CPS <10	X																																PD-L1 IHC 22C3 pharmDx assay is required for PD-L1 testing to calculate CPS; in the case 22C3 testing cannot be done locally, central testing has to be performed

Study Period	Screening	Treatment Period Cycle = 42 days																											Notes
Visit Timing	Up to 28 days prior to 1st dose	Cycle 1								Cycles 2							Cycle 3							Cycle 4							Every 9 weeks	Cycle ≥5	
Visit Window (Days)	-28 to -1	1	2	3	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36	1	2	8	15	22	29	36		1/8/15/ 22/29/36	
Post-Treatment Tumor Biopsy (optional)												X																					Requested between Day 8 and Day 15 of Cycle 2.
CCI [redacted]																																	

1. Laboratory test at screening are to be performed within 7 days before the first dose of study treatment.
2. Procedure/sample collection may be performed up to 72 hours before the first dose of study treatment. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point.
3. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.

2.7 Schedule of Activities for the End of Treatment and Post-Treatment Follow-Up Periods – Dose Escalation and Confirmation Phase and Dose Expansion Phase

Study Period	End of Treatment	Post-Treatment Follow-Up			Notes
		Safety	Disease Status[1]	Survival[2]	
Visit Timing	Treatment discontinuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)		+/-14	+/-7	+/-14	
Administrative / Clinical Procedures / Assessments					
Concomitant Medication	X	X			
Physical Examination	X	X			A directed physical examination may be done unless a full examination is deemed necessary.
Weight	X	X			
Vital Signs	X	X			Measurements include temperature, pulse, respiratory rate, blood pressure.
ECOG Performance Status	X	X			
Adverse Event Monitoring	X	X	X		After treatment discontinuation, participants will be monitored for AEs for 30 days and SAEs for 90 days (30 days if the participant initiates new anticancer therapy). Participants with an ongoing AE at the time of treatment discontinuation will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
Tumor Imaging and Response Assessment			X		Post-treatment tumor imaging every 9 weeks starting from the first dose of study treatment.
New Anticancer Therapy Status		X	X	X	
Survival Status	←	→		X	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study. After confirmed disease progression, each participant will be contacted by telephone for survival until participant withdrawal of consent, becoming lost to follow-up, death, or the end of the study.
Laboratory Procedures/Assessments – LOCAL					
Hematology	X	X			
Chemistry Panel	X	X			
Thyroid Function Testing (T4, T3, TSH)		X			

Study Period	End of Treatment	Post-Treatment Follow-Up			Notes
		Safety	Disease Status[1]	Survival[2]	
Visit Timing	Treatment discontinuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)		+/-14	+/-7	+/-14	
Laboratory Procedures/Assessments – CENTRAL					
CCI [redacted]					
Blood for circulating tumor DNA (ctDNA) Analysis	X				To be collected at End of Treatment visit.

1. Participants who discontinue study treatment for reasons other than confirmed disease progression will have post-treatment follow-up imaging every 9 weeks for disease status until disease progression, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, or death.
2. Participants should be contacted for their first scheduled survival follow-up 12 weeks after the Post-Treatment Safety Follow-Up visit.
3. Arms 3, 1a (anti-MK-5890 antibody and pharmacokinetic sampling for MK-5890 only), 2a, 2b, 2c, and 4 only.

2.8 Schedule of Activities for the Cross-Over Treatment Phase – Dose Escalation and Confirmation Phase (Arm 1) and Dose Expansion Phase (Arm 1a)

Participants who discontinue MK-5890 in the monotherapy arms (Arm 1 and Arm 1a) due to disease progression may, at the investigator's discretion and after consultation with the Sponsor, cross-over to MK-5890 + pembrolizumab combination treatment. The list and schedule of procedures to be performed are provided in the following chart.

Study Period / Treatment Cycle	Treatment Period[1, 2, 3] Cycle = 21 days					End of Treatment	Post-Treatment Follow-Up Period			Notes
	Cycle 1			Cycles ≥2			Safety	Disease Status[4]	Survival[5]	
Visit Timing / Cycle Day	1	8	15	1	Every 9 weeks	Treatment dis-continuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)		+/- 2	+/- 3		+/-7		+/-14	+/-7	+/-14	
Administrative Procedures										
Informed Consent	X									Participants must be re-consented and the risks and benefits of continuing treatment after disease progression should be reviewed prior to performing any cross-over-related procedures.
Concomitant Medication	X			X		X	X			
Clinical Procedures/Assessments										
Physical Examination	X[6]			X[6]		X	X			A full physical examination should be done at Cycle 1 and at the End of Treatment visit. Directed physical examinations may be done at the other time points unless a full examination is deemed necessary.
Weight	X			X		X	X			
Vital Signs	X			X		X	X			Measured prior to dosing, and 2 hours, 4 hours, and 6 hours after the start of the MK-5890 infusion on Day 1 of Cycle 1. In Cycles ≥2, measured prior to dosing on Day 1 only. Also measured at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit.
ECOG Performance Status	X[6]			X[6]		X	X			On Day 1, should be performed prior to dosing.
12-Lead Electrocardiogram	X[6]			X						Performed prior to dosing and within 30 minutes after the end of the MK-5890 infusion on Day 1 of Cycles 1-4.

Study Period / Treatment Cycle	Treatment Period[1, 2, 3] Cycle = 21 days					End of Treatment	Post-Treatment Follow-Up Period			Notes
	Cycle 1			Cycles ≥2			Safety	Disease Status[4]	Survival[5]	
Visit Timing / Cycle Day	1	8	15	1	Every 9 weeks	Treatment dis-continuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)		+/- 2	+/- 3		+/-7		+/-14	+/-7	+/-14	
CCI [redacted]										
Adverse Event Monitoring	X			X		X	X	X		Continuous AE reporting from the time of treatment allocation. After treatment discontinuation, participants will be monitored for AEs for 30 days and SAEs for 90 days (30 days if the participant initiates new anticancer therapy). Participants with an ongoing AE at the time of treatment discontinuation will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
Tumor Imaging and Response Assessment					X			X		Every 9 weeks from the first dose of combination treatment.
New Anticancer Therapy Status							X	X	X	
Survival Status	←								→	X	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study. After confirmed disease progression, each participant will be contacted by telephone for survival until participant withdrawal of consent, becoming lost to follow-up, death, or the end of the study.

Study Period / Treatment Cycle	Treatment Period[1, 2, 3] Cycle = 21 days					End of Treatment	Post-Treatment Follow-Up Period			Notes
	Cycle 1			Cycles ≥2			Safety	Disease Status[4]	Survival[5]	
Visit Timing / Cycle Day	1	8	15	1	Every 9 weeks	Treatment dis-continuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)		+/- 2	+/- 3		+/-7		+/-14	+/-7	+/-14	
Laboratory Procedures/Assessments – LOCAL										
Hematology	X[6]	X	X	X[6]		X	X			To be collected prior to dosing and 4 hours after the start of the MK-5890 infusion on Day 1, and once daily on Day 8 and Day 15 of Cycle 1. In Cycles ≥2, to be collected prior to dosing on Day 1 only. Samples also to be collected at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit.
Chemistry Panel	X[6]	X	X	X[6]		X	X			
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[6]			X[6]						
Thyroid Function Testing (T4, T3, TSH)	X[6]			X[6]			X			To be collected on Day 1 of Cycle 1, every other cycle thereafter, and at the Post-Treatment Safety Follow-Up visit.
Laboratory Procedures/Assessments – CENTRAL										
CCI [redacted]										
Serum for Biomarker Analyses	X			X						MK-5890 infusion on Day 1.

Study Period / Treatment Cycle	Treatment Period[1, 2, 3] Cycle = 21 days					End of Treatment	Post-Treatment Follow-Up Period			Notes
	Cycle 1			Cycles ≥2			Safety	Disease Status[4]	Survival[5]	
Visit Timing / Cycle Day	1	8	15	1	Every 9 weeks	Treatment dis-continuation	30 days after the last dose	Every 9 weeks	Every 12 weeks	
Visit Window (Days)		+/- 2	+/- 3		+/-7		+/-14	+/-7	+/-14	
Peripheral Blood Mononuclear Cell (PBMC) Collection for Biomarker Analyses	X			X		X				To be collected prior to dosing on Day 1 of Cycle 1, every 4 cycles thereafter, and requested at the End of Treatment visit.
Blood for Immunophenotyping	X			X		X				To be collected prior to dosing on Day 1 of each cycle, and requested at the End of Treatment visit.
CCI										CCI
Serum for Soluble Receptor Analysis	X			X						

1. Any participant receiving anticoagulant therapy should have coagulation factors (PT/INR and aPTT) monitored closely throughout the study.
2. For women of childbearing potential, monthly pregnancy testing should be conducted per local regulations where applicable. If a urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test is required.
3. Participants will be requested to provide a post-treatment tumor biopsy sample between Day 8 and Day 15 of Cycle 2. Leftover tissue may also be saved for future biomedical research (FBR) if the participant signed the FBR consent.
4. Participants who discontinue study treatment for reasons other than confirmed disease progression will have post-treatment follow-up imaging every 9 weeks for disease status until disease progression, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, or death.
5. Participants should be contacted for their first scheduled survival follow-up 12 weeks after the Post-Treatment Safety Follow-Up visit.
6. Procedure/sample collection may be performed up to 72 hours before the first dose of study treatment. Procedures/sample collections performed for the End of Treatment visit done within this timeframe in the monotherapy arm do not need to be repeated for the cross-over Cycle 1, Day 1 time point.
7. Participants who crossed-over from Arm 1a only.

3. INTRODUCTION

MK-5890 is a humanized, agonist mAb that binds to the immunomodulatory receptor, CD27, providing a co-stimulatory signal that enhances T cell receptor-mediated cellular responses. This humanized IgG1 antibody is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with pembrolizumab (a humanized anti-PD-1 receptor mAb) to increase benefit to patients with various tumor types.

3.1 Study Rationale

MK-5890 is being developed for the treatment of solid tumors. This is the first-in-human study of MK-5890 and is designed to assess the safety, tolerability, PK, and PD of escalating doses of MK-5890 when used as monotherapy and in combination with pembrolizumab in participants with advanced solid tumors who have received or been intolerant to all treatment known to confer clinical benefit. The effect of MK-5890 on tumor size will also be explored.

In addition, the Arm 3 cohort in the dose escalation/dose confirmation phase of the study will assess the safety and tolerability of treatment with MK-5890 in combination with pembrolizumab and standard chemotherapy in participants with nonsquamous NSCLC.

The dose expansion phase of the study will further examine safety and exploratory efficacy of MK-5890 when used as monotherapy and in combination with pembrolizumab in specific tumor types as described in Inclusion Criterion 1 (Section 6.1).

In addition, the Arm 4 cohort in the dose expansion phase of the study will assess the safety and tolerability and efficacy of treatment with MK-5890 in combination with pembrolizumab and standard chemotherapy in participants with locally recurrent inoperable TNBC cancer not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC whose tumor PD-L1 CPS is less than 10.

3.2 Background

Refer to the Investigator's Brochures (IBs) for detailed background information on MK-5890 and pembrolizumab.

3.2.1 Pharmaceutical and Therapeutic Background

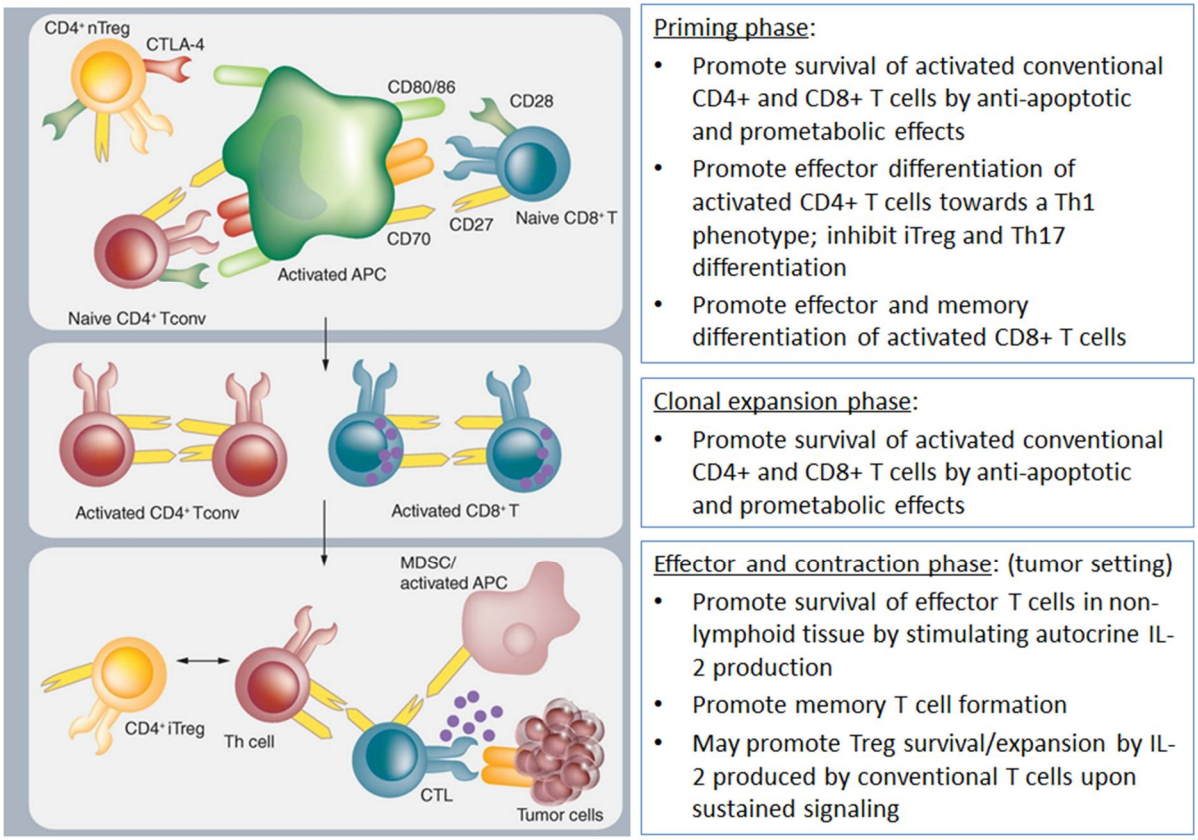
3.2.1.1 MK-5890 Background

MK-5890 is a CD27 agonist antibody being developed as a novel cancer immunotherapeutic agent with an initial focus to increase benefit to patients with treatment-refractory malignancies. CD27 is a co-stimulatory member of the TNF receptor superfamily, which is constitutively expressed on naïve, activated and memory T cells, NK T cells, memory B cells, and a subset of NK cells [Nolte, M. A., et al 2009] [Borst, J., et al 2005] [Lens, S. M., et al 1998]. CD27 signaling is regulated through strict control of expression of its ligand, CD70, which is transiently expressed on activated T and B cells, primed dendritic cells,

NK cells, and dendritic and epithelial cells of the thymic medulla [Nolte, M. A., et al 2009] [Coquet, J. M., et al 2013] [Hishima, T., et al 2000] [Kashii, Y., et al 1999] [Orengo, A. M., et al 1997].

CD27 signaling plays an important role in both generation and maintenance of cytotoxic T lymphocyte responses and in survival of activated T cells after they traffic to non-lymphoid organs (Figure 1). Given that CD27 signaling enhances priming of cytotoxic T lymphocyte responses even in the absence of primed antigen presenting cells [Ahrends, T., et al 2016], the CD27 agonistic activity can be exploited as an immunotherapeutic approach for cancers with minimal T cell infiltrate and/or inadequate responses. In combination with anti-PD-1 or other immune checkpoint inhibitors, CD27 signaling can be used to protect newly generated T cells in the tumor. This rationale has been supported by pre-clinical data from human CD27 knock-in mouse model syngeneic tumor studies showing efficacy of MK-5890 as both a monotherapy and in combination with anti-PD-1.

Figure 1 Mechanism of Action of the CD27/CD70 Co-Stimulatory System in Regulation of the T Cell Response



Adapted from van de Ven and Borst 2015 [van de Ven, K. 2015]

3.2.1.2 Pembrolizumab (MK-3475) Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are Type I transmembrane glycoproteins containing an Ig variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in a variety of cancers.

3.2.2 Pre-Clinical and Clinical Studies

3.2.2.1 MK-5890 Pre-Clinical and Clinical Studies

Pre-clinical studies of MK-5890 are described in the IB. This is the first clinical study of MK-5890.

3.2.2.2 Pembrolizumab (MK-3475) Pre-Clinical and Clinical Studies

Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy, both as monotherapy and combination therapy, for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications, refer to the IB and Physician Circular.

3.2.3 Ongoing Clinical Studies

3.2.3.1 MK-5890 Ongoing Clinical Studies

This study represents the first-in-human use of MK-5890.

3.2.3.2 Pembrolizumab Ongoing Clinical Studies

Over 400 interventional clinical studies involving pembrolizumab are currently ongoing in a number of advanced solid tumor indications, as well as in hematological malignancies.

3.2.4 Information on Other Study-Related Therapy

Participants with nonsquamous NSCLC enrolled as part of Amendment 02 will receive concomitant chemotherapy with pemetrexed and carboplatin as per their product labels. Refer to their respective package inserts for more information.

Participants with locally recurrent inoperable TNBC not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC whose tumor PD-L1 CPS is less than 10 enrolled as part of Amendment 03 will receive concomitant chemotherapy with nab-paclitaxel as per its product labels. Refer to its respective package inserts for more information.

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 IB and informed consent documents.

4. OBJECTIVES/HYPOTHESES AND ENDPOINTS

In male and female participants with advanced solid tumors who are at least 18 years of age:

Objectives	Endpoints
Primary	
• Objective: To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-5890 when used as monotherapy and in combination with pembrolizumab in the dose escalation and confirmation phase and the dose expansion phase	• Number of participants with a dose-limiting toxicity (DLT) • Number of participants with ≥1 adverse event (AE) • Number of participants who discontinue study treatment due to an AE

Objectives	Endpoints
Secondary	
• Objective: To evaluate the PK of MK-5890 when given by IV infusion as monotherapy, in combination with pembrolizumab, in combination with pembrolizumab, pemetrexed, and carboplatin, and in combination with pembrolizumab and nab-paclitaxel, in the dose escalation and confirmation phase and/or the dose expansion phase	• PK parameters including area under the curve (AUC), minimum concentration (C_{min}), and maximum concentration (C_{max})
• Objective: To evaluate the objective response rate (ORR) of MK-5890 when used as monotherapy, in combination with pembrolizumab, in combination with pembrolizumab and nab-paclitaxel in the dose expansion phase	• ORR as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)
• Objective: To determine the safety and tolerability of MK-5890 in combination with pembrolizumab, pemetrexed, and carboplatin in participants with nonsquamous NSCLC and to establish maximum tolerated doses (MTDs) of carboplatin and pemetrexed when used in combination with MK-5890 and pembrolizumab	• Number of participants with a DLT • Number of participants with ≥1 AE • Number of participants who discontinue study treatment due to an AE
• Objective: To determine the safety and tolerability of MK-5890 in combination with pembrolizumab and nab-paclitaxel in participants with locally recurrent inoperable TNBC cancer not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC and to establish MTDs of nab-paclitaxel when used in combination with MK-5890 and pembrolizumab	• Number of participants with a DLT • Number of participants with ≥1 AE • Number of participants who discontinue study treatment due to an AE

Objectives	Endpoints
Tertiary/Exploratory	
• Objective: To evaluate the preliminary antitumor activity of MK-5890 when used as monotherapy, in combination with pembrolizumab, and in combination with pembrolizumab, pemetrexed, and carboplatin in the dose escalation and confirmation phase	• ORR and progression-free survival (PFS) as assessed by the investigator based on RECIST 1.1 and modified RECIST 1.1 for immune-based therapeutics (iRECIST) [Seymour, L., et al 2017], and overall survival (OS)
• Objective: To evaluate the antitumor activity of MK-5890 when used as monotherapy, in combination with pembrolizumab, in combination with pembrolizumab and nab-paclitaxel, in the dose expansion phase	• ORR as assessed by the investigator based on iRECIST, and PFS as assessed by the investigator based on RECIST 1.1 and iRECIST, and OS
• Objective: To evaluate development of circulating anti-MK-5890 antibodies and anti-pembrolizumab antibodies, as appropriate, following administration of MK-5890 monotherapy, MK-5890 in combination with pembrolizumab, in combination with pembrolizumab and nab-paclitaxel, and MK-5890 in combination with pembrolizumab, pemetrexed, and carboplatin, in the dose escalation and confirmation phase and/or the dose expansion phase	• Circulating anti-MK-5890 and anti-pembrolizumab antibody levels
• Objective: To evaluate the PK of pembrolizumab when used in combination with MK-5890, the PK of pembrolizumab, pemetrexed, and carboplatin when used in combination with MK-5890, and the PK of pembrolizumab when used in combination with MK-5890 with nab-paclitaxel in the dose escalation and confirmation phase and/or the dose expansion phase	• PK parameters including AUC, C_{min}, and C_{max}

Objectives	Endpoints
CCI [redacted]	CCI [redacted]

5. STUDY DESIGN

5.1 Overall Design

This is a first-in-human, multi-site, open-label, dose escalation, dose confirmation, and dose expansion study of MK-5890 when used as monotherapy and/or in combination with pembrolizumab in participants with a histologically or cytologically confirmed diagnosis of advanced solid tumor who have received or been intolerant to all treatment known to confer clinical benefit. The study will include 2 parts: a dose escalation and confirmation phase (Section 5.5.6) and a dose expansion phase to further examine safety and exploratory efficacy of MK-5890 when used as monotherapy and in combination with pembrolizumab and chemotherapy in specific tumor types (Section 5.5.7).

The dose escalation and confirmation phase of the study will use a mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% to identify a preliminary RP2D of MK-5890 when used as monotherapy (Arm 1) and in combination with pembrolizumab (Arm 2). Participants will be allocated by non-random assignment to a treatment arm using an interactive voice response system/integrated web response system (IVRS/IWRS). Study treatment will be administered by IV infusion on Day 1 of each 21-day cycle for up to a maximum of 35 cycles.

Six pre-determined dose levels of MK-5890 will be explored independently in each treatment arm. It may be acceptable to de-escalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. The dose of pembrolizumab in Arm 2 will remain constant at 200 mg. There will be no intraparticipant dose escalation for participants enrolled in this study except as described in Section 7.2.3.

Enrollment into the MK-5890 + pembrolizumab combination treatment arm (Arm 2) will begin once all participants at the second dose level in the MK-5890 monotherapy arm (Arm 1) complete the DLT evaluation period and a dose escalation decision has been made.

When both treatment arms are open for enrollment, IVRS/IWRS will alternate participant assignment between Arms 1 and 2 starting with Arm 1. An observation period of at least 24 hours will occur between treatment initiation in the first 3 participants enrolled within each dose level. Each new dose cohort will open for enrollment without delay once the 21-day DLT evaluation period of the previous dose cohort is completed and a dose escalation decision has been made.

During dose escalation, a minimum of 3 participants are required at each dose, and up to 6 participants may be enrolled initially at each new dose. As outlined in Table 4, based on the mTPI design, the number of participants who are enrolled at a dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining participants who are at risk of developing a DLT before the dose would be considered unacceptably toxic.

Dose escalation and confirmation will end after 14 participants have been treated at any of the selected doses (including intermediate doses) as long as the decision based on Table 4 is to stay. The pool-adjacent-violators algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses in each treatment arm under the assumption of monotonicity between DLT rates and dose levels. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RP2D, however, the totality of the data will also be considered. The preliminary RP2D of MK-5890 in the combination arm (Arm 2) will not exceed, but may equal, the preliminary RP2D in the MK-5890 monotherapy arm (Arm 1).

In addition to testing MK-5890 as monotherapy and combination treatment with pembrolizumab in participants with advanced solid tumors, the dose escalation and confirmation phase will also include a cohort of participants with nonsquamous NSCLC who will be treated with CCI MK-5890 in combination with 200 mg pembrolizumab, 500 mg/m^2 pemetrexed, and AUC 5 mg/mL/min carboplatin for up to 4 cycles followed by maintenance therapy with MK-5890, pembrolizumab, and pemetrexed (Arm 3). MK-5890 will be given for up to a total of 6 months. Pembrolizumab and pemetrexed will be given for up to a total of 35 cycles with the possibility of continuing pemetrexed during the follow-up phase of the study at the discretion of the investigator per standard of care. All treatments will be given by IV infusion once every 3 weeks (Q3W). For participants who continue pemetrexed after 35 cycles, pemetrexed will not be considered a new anticancer therapy. In the event of unacceptable toxicity during the chemotherapy combination, the doses of chemotherapy will be de-escalated according to the rules outlined in the mTPI design (Table 4). The chemotherapy doses that will be tested are outlined in Table 3. Dose finding will end after 10 participants have been treated at a dose level of the chemotherapy combination as long as the decision based on Table 4 is to stay or escalate. Arm 3 may stop early if the number of DLTs exceeds an acceptable rate while at the lowest possible dose combination.

The dose expansion phase will assess the safety and antitumor efficacy of CCI MK-5890 in combination with 200 mg pembrolizumab, both given Q3W in 15 to 30 participants with triple-negative breast cancer (TNBC; [Arm 2a]) using an adaptive design. In the adaptive design, the totality of the data will be examined once the first 15 participants with TNBC are enrolled and have at least 1 post-baseline scan to decide whether or not to continue

enrollment to 30 participants. [redacted]. Enrollment will not be held after the first 15 participants; data will be analyzed on an ongoing basis.

The dose expansion phase will also assess the safety and antitumor efficacy of [redacted] MK-5890 given Q3W as monotherapy (Arm 1a), 30 mg MK-5890 in combination with 200 mg pembrolizumab, both given Q3W (Arm 2b), and 30 mg MK-5890 in combination with 400 mg pembrolizumab, both given once every 6 weeks (Q6W; Arm 2c) in 60 participants with endometrial cancer (20 participants per arm) using an adaptive design. Participants with endometrial cancer will be randomized at a 1:1:1 ratio to an arm using IVRS/IWRS. In the adaptive design, the totality of the data will be examined once the first 10 participants with endometrial cancer per treatment arm are enrolled and have at least 1 post-baseline scan to decide whether or not to continue enrollment to 20 participants in that arm. [redacted] Enrollment will not be held after the first 10 participants per treatment arm; data will be analyzed on an ongoing basis.

In addition, the dose expansion phase will assess the safety and antitumor efficacy of [redacted] MK-5890 in combination with 400 mg pembrolizumab and 100 mg/m^2 nab-paclitaxel; MK-5890 and pembrolizumab given Q6W up to 18 cycles (approximately 2 years) and nab-paclitaxel will be administered on a 3-week on (Days 1, 8, and 15)/1-week off schedule every 28 days (Arm 4), in participants with locally recurrent inoperable TNBC not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC whose tumor PD-L1 CPS is less than 10. This cohort will first evaluate the safety with 10 participants. In the event of unacceptable toxicity, the doses of nab-paclitaxel will be de-escalated according to the rules outlined in the mTPI design (Table 4). The nab-paclitaxel doses that will be tested are outlined in Table 3. Dose finding will end after 10 participants have been treated at a dose level of the chemotherapy combination as long as the decision based on Table 4 is to stay or escalate. Arm 4 may stop early if the number of DLTs exceeds an acceptable rate while at the lowest possible dose combination. After Arm 4 has demonstrated a tolerable safety profile, additional 30 participants will be enrolled at the tolerable dose level for further efficacy evaluation. In the adaptive design, the totality of the data will be examined once the first 20 participants at the tolerable dose level are enrolled (including the 10 participants for safety evaluation) and have at least 1 post-baseline scan to decide whether or not to continue enrollment to 40 participants in Arm 4. [redacted] Enrollment will not be held after the first 20 participants enrolled; data will be analyzed on an ongoing basis.

In Arm 1a, MK-5890 will be given for up to 35 cycles. In Arms 2a and 2b, MK-5890 will be given for up to 6 months and pembrolizumab will be given for up to 35 cycles. In Arm 2c and Arm 4, MK-5890 and pembrolizumab will be given for up to 18 cycles.

The doses/schedules of MK-5890 to be tested in the dose expansion phase were determined using the totality of the available data from the dose escalation and confirmation phase.

The Sponsor may prematurely terminate enrollment into a tumor type for administrative reasons; in such cases, the sites will be notified via an administrative letter. All participants already enrolled or in the screening period will be allowed to continue in the study.

Participants in all phases of the study will receive study treatment until disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements, the participant completes study treatment (see Section 8.1 for details), administrative reasons requiring cessation of treatment, or death, whichever occurs first.

Participants in the dose escalation and confirmation and dose expansion phases of the study who discontinue MK-5890 in the monotherapy arm due to disease progression may, at the investigator's discretion and after consultation with the Sponsor, cross-over to MK-5890 + pembrolizumab combination treatment (Section 7.2.3).

After treatment discontinuation, participants will be monitored for AEs for 30 days and serious adverse events (SAEs) for 90 days (30 days if the participant initiates new anticancer therapy). Participants with an ongoing AE at the time of treatment discontinuation will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Participants who discontinue study treatment for reasons other than confirmed disease progression will have post-treatment follow-up imaging every 9 weeks for disease status until disease progression, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, or death, whichever occurs first.

After confirmed disease progression, each participant will be contacted by telephone approximately every 12 weeks for survival until participant withdrawal of consent, becoming lost to follow-up, death, or the end of the study, whichever occurs first.

Final RP2D(s) for MK-5890 will be determined using PK and PD endpoints, as well as all available safety data, including DLT rates and the cumulative incidence of late toxicities (ie, toxicities that occur after the 21-day DLT evaluation period) from participants in all phases of the study.

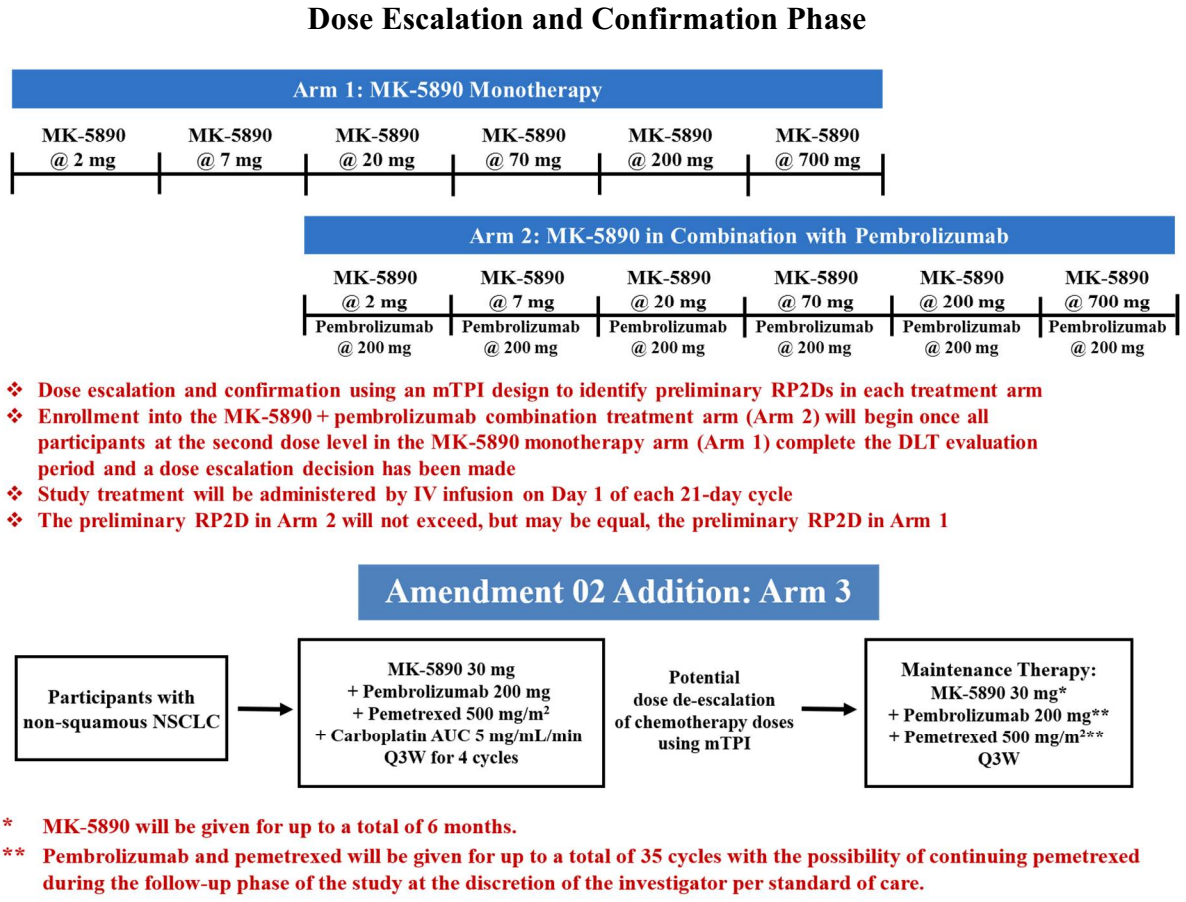
The study will be conducted in conformance with Good Clinical Practice (GCP). Adverse events will be evaluated according to criteria outlined in the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 or later.

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.

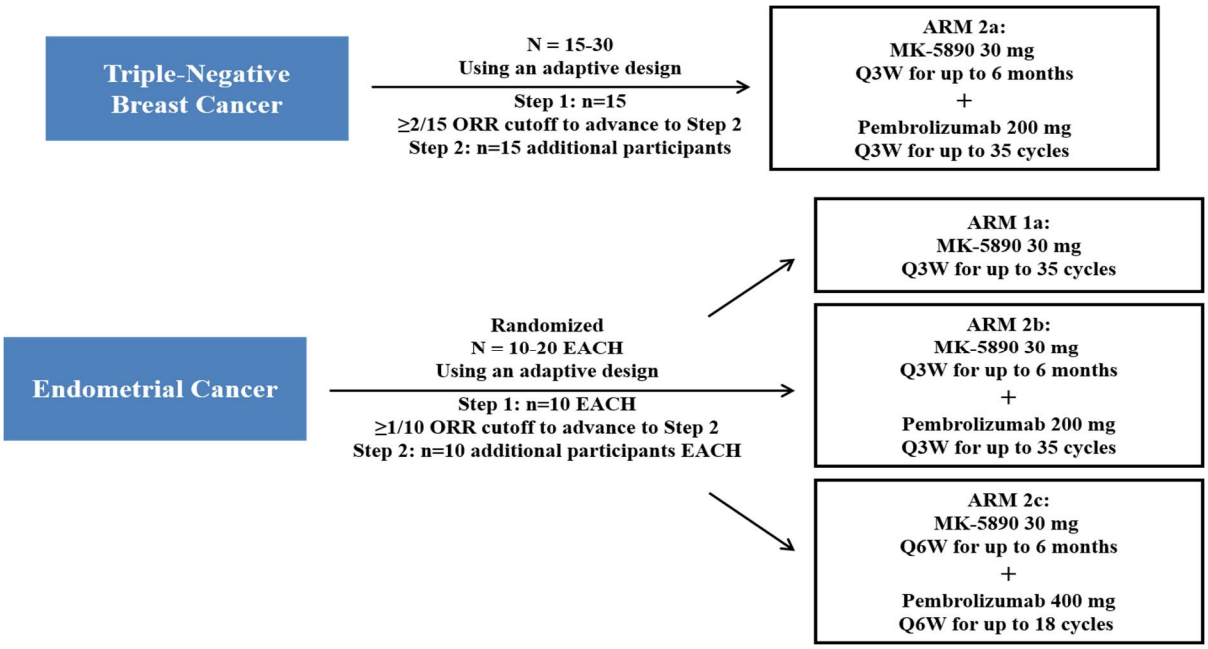
5.1.1 Study Diagram

The study design is depicted in Figure 2.

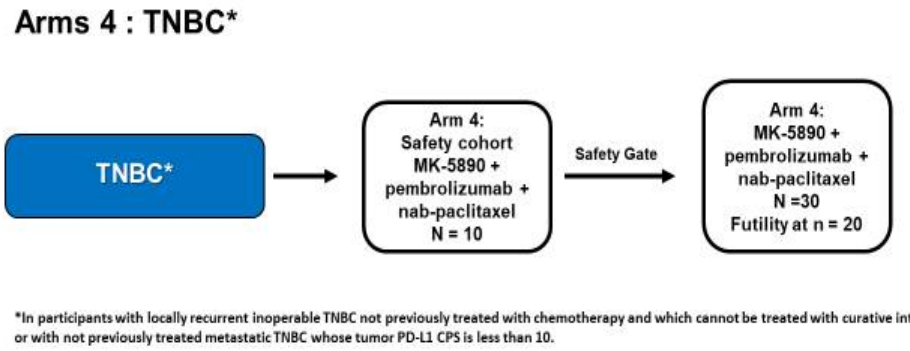
Figure 2 Study Design



Dose Expansion Phase



❖ **Enrollment of additional participants to further examine safety and exploratory efficacy in specific tumor types**



IV=intravenous; mTPI=modified toxicity probability interval; ORR=objective response rate; RP2D=recommended Phase 2 dose; Q3W=once every 3 weeks; Q6W=once every 6 weeks; TNBC=triple negative breast cancer

5.2 Number of Participants

This study is expected to enroll approximately 202 participants.

5.3 Beginning and End of Study Definition

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

5.3.1 Clinical Criteria for Early Study Termination

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

1. The incidence or severity of adverse drug reactions in this, or other, studies suggest a potential health hazard to participants;
2. Plans emerge to modify or discontinue the development of the study drug;
3. There is poor adherence to the protocol and/or regulatory requirements; and/or
4. The quality or quantity of data recording is inaccurate or incomplete.

Ample notification will be provided to the sites if the Sponsor decides not to continue to supply MK-5890 and/or pembrolizumab.

5.4 Scientific Rationale for Study Design

MK-5890 is being developed for the treatment of solid tumors. This is the first-in-human study of this antibody and is designed to assess the safety, tolerability, PK, and PD of escalating doses of MK-5890 when used as monotherapy and in combination with pembrolizumab in participants with advanced/refractory solid tumors. The effect of MK-5890 on tumor size will also be explored. The anti-CD27 agonistic activity of MK-5890 has been studied in syngeneic mouse tumor models. Administration of this antibody was associated with regression of established solid tumors and systemic immune response. Preclinical efficacy data demonstrated that the combination of anti-CD27 and anti-PD-1 antibodies resulted in improved antitumor efficacy. For detailed data from the pre-clinical studies, please refer to the IB.

Selection of particular tumor types for the dose expansion phase of the study was based on multiple factors including all available clinical and preclinical data, the current therapeutic landscape, and the unmet medical need for more efficacious therapies. TNBC represents a tumor with high inflammatory phenotype but at the same time low response rate for therapy with immune checkpoint inhibitors. Given the mechanism of action of MK-5890, stimulation of tumor residing T cells can potentially energize antitumor activity when combined with immune checkpoint inhibitors. The early efficacy signal observed in endometrial cancer in the MK-5890 monotherapy arm of the dose escalation and confirmation phase helped select this tumor type for expansion.

Addition of Chemotherapy to MK-5890 Plus Pembrolizumab Combination

The Arm 3 cohort in the dose escalation/dose confirmation phase of the study will assess the safety and tolerability of treatment with MK-5890 in combination with pembrolizumab and standard chemotherapy in participants with non-squamous NSCLC.

The Arm 4 cohort will test safety/tolerability and antitumor activity of MK-5890 in combination with pembrolizumab and nab-paclitaxel in participants with locally recurrent inoperable TNBC not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC whose tumor PD-L1 CPS is less than 10.

Preclinical and clinical evidence suggest that conventional chemotherapies reactivate antitumor immune responses by increasing immunogenic cell death and antigen release, and/or by inhibiting immunosuppressive factors in the tumor microenvironment [Emens, L. A. and Middleton, G. 2015] [Galluzzi, L., et al 2015] [Vincent, J., et al 2010]. Further, chemotherapies can enhance tumor antigen presentation by upregulating the expression of either tumor T cell receptors (TCRs) themselves, or the MHC1 molecules to which the TCRs bind [Emens, L. A. and Middleton, G. 2015]. A substantial body of clinical evidence has emerged to suggest that the efficacy of immunotherapy, including PD-1 blockade with pembrolizumab, can be enhanced by chemotherapy [Langer, C. J., et al 2016] [Gandhi, L., et al 2018]. There is no clinical data for the combination of MK-5890 or other anti-CD27 antibodies with chemotherapeutic agents to date. This study will test the safety and tolerability of MK-5890 plus pembrolizumab in combination with pemetrexed and carboplatin in patients with non-squamous NSCLC or in combination with nab-paclitaxel in participants with locally recurrent inoperable TNBC not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC whose tumor PD-L1 CPS is less than 10. In the event of unacceptable toxicity during the chemotherapy combination, the doses of chemotherapy will be de-escalated according to the rules outlined in the mTPI design using the standard dose modification guidelines for these regimens. The rationale for de-escalating the doses of chemotherapies is that maximum doses of chemotherapeutic agents are defined by MTDs, with doses limited by the rate of DLTs. Biologics are not typically MTD-limited. In this study, DLTs have been observed in association with infusion-related reactions, but not with other adverse events during dose escalation, whether alone or in combination with pembrolizumab. In an attempt to manage occurrence of infusion-related reactions, a recommendation to premedicate participants was made. If the triple combination is tolerable and doses of chemotherapy are determined, the safety and efficacy of this triple combination in patients with NSCLC and TNBC may be further evaluated in a separate study. The overall intention is to determine whether addition of MK-5890 to pembrolizumab and chemotherapy provides superior efficacy benefit to combination of immune checkpoint inhibitor and chemotherapy, which is a current standard of care treatment for patients with untreated advanced NSCLC of nonsquamous histology and TNBC.

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

Efficacy endpoints include ORR, PFS, and OS and are secondary and tertiary/exploratory endpoints in this study. Tumor response will be assessed by investigators using RECIST 1.1 and iRECIST.

Immune-modified RECIST 1.1 for immune-based therapeutics [Seymour, L., et al 2017] accounts for the unique tumor response characteristics seen with immunotherapeutic agents. iRECIST was developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency.

Immunotherapeutic agents such as MK-5890 and pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may, thus, not provide an accurate response assessment of immunotherapeutic agents. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

The unidimensional measurement of target lesions, qualitative assessment of non-target lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. If a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. In this study, iRECIST will be used by investigators to assess tumor response and progression, and make treatment decisions.

5.4.1.2 Safety Endpoints

The primary objectives of this study include characterizing the safety and tolerability of MK-5890 when used as monotherapy and in combination with pembrolizumab in participants with advanced solid tumors. Secondary objectives include determining the safety and tolerability of MK-5890 in combination with pembrolizumab, pemetrexed, and carboplatin in participants with nonsquamous NSCLC. The secondary objectives also include determining the safety and tolerability of MK-5890 in combination with pembrolizumab and nab-paclitaxel in participants with locally recurrent inoperable TNBC not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC whose tumor PD-L1 CPS is less than 10.

The primary safety analyses will be based on the number of participants who experience toxicities as defined by the NCI CTCAE, version 4.0 or later.

The attribution to study treatment, time of onset, duration of the event, resolution of the event, and any concomitant medications administered as a result of the event will be

recorded. Safety data will include, but are not limited to, AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as events of clinical interest (ECIs) as described in Section 9.3.7.

5.4.1.3 CCI [redacted]

CCI [redacted]

5.4.1.4 CCI [redacted]

CCI [redacted]

5.4.1.5 CCI [redacted]

CCI [redacted]

5.4.1.6 CCI [redacted]

CCI [redacted]

5.4.1.6.1 CCI [redacted]

CCI [redacted]

5.4.1.6.2 CCI [redacted]

CCI [redacted]

5.4.1.6.3 CCI [redacted]

CCI [redacted]

5.4.1.6.4 CCI [redacted]

CCI [redacted]

CCI [redacted]

5.4.1.6.5 CCI [redacted]

CCI [redacted]

5.4.1.6.6 CCI [redacted]

CCI [redacted]

CCI [redacted]

5.4.2 Rationale for The Use of Comparator/Placebo

No comparator/placebo is proposed for this study.

5.5 Justification for Dose

5.5.1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

CCI

CCI

[redacted]

CCI

[redacted]

5.5.2 CCI

CCI

5.5.3 CCI

5.5.3.1 CCI

CCI

CCI

[redacted]

5.5.3.2 Pembrolizumab (MK-3475)

The planned dose of pembrolizumab for Arms 2, 3, 2a, and 2b of this study is 200 mg given Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg given Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type.

In Arms 2c and 4, pembrolizumab will be given at a dose of 400 mg Q6W. Based on the robust understanding of pembrolizumab clinical pharmacology, including well-established exposure-response profiles over a 5-fold dose range (dataset of 2993 participants), a 400 mg Q6W dosing regimen is expected to produce similar efficacy and safety in all clinical treatment settings where 200 mg (or 2 mg/kg) Q3W pembrolizumab dosing is currently approved.

5.5.4 Rationale for Pemetrexed and Carboplatin Doses in NSCLC

The starting doses of chemotherapies in this study: 500 mg/m^2 pemetrexed and AUC 5 mg/mL/min carboplatin, both administered by IV infusion Q3W for up to 4 cycles, with the possibility of maintenance therapy with pemetrexed at the discretion of the investigator, represent the standard of care per the approved product labels.

5.5.5 Rationale for Nab-paclitaxel Doses in Previously Untreated Metastatic TNBC

Nab-paclitaxel is a combination of albumin and paclitaxel that forms particles of a mean 130 nm in diameter. Unlike previous taxanes, the nab-paclitaxel formulation is solvent-free and does not require premedication to prevent solvent-related hypersensitivity reactions. It received US FDA approval in 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy (prior therapy should have included an anthracycline, unless clinically contraindicated). Nab-paclitaxel is also approved in the EU as 2L monotherapy for mBC. These approvals were based on a randomized Phase 3 study, which compared nab-paclitaxel 260 mg/m^2 Q3W to paclitaxel 175 mg/m^2 Q3W with corticosteroid or antihistamine premedication [Gradishar, W. J., et al 2005]. Treatment with nab-paclitaxel led to a significantly higher ORR compared with paclitaxel based on the ITT population (33% versus 19%, respectively; $p = 0.001$). The ORR was also significantly higher in participants who received nab-paclitaxel as 1L therapy (42% versus 27%; $p = 0.029$) or 2L and above (2L+) therapy (27% versus 13%; $p = 0.006$). Participants who received nab-paclitaxel had a 25% lower risk of progression compared with those receiving paclitaxel (HR 0.75; $p = 0.006$). The incidence of Grade 4 neutropenia was significantly lower with nab-paclitaxel treatment (9% versus 22%, respectively; $p < 0.001$). Nab-paclitaxel was associated with higher incidence of Grade 3 sensory neuropathy (10% versus 2%; $p < 0.001$), which improved to ≤Grade 2 in

about 3 weeks. Nab-paclitaxel demonstrated a statistically significant improvement in OS in participants who received it as 2L+ therapy (56.4 versus 46.7 weeks; $p = 0.024$), but only a modest, nonsignificant OS difference in the ITT population (65 versus 56 weeks; $p = 0.374$). In addition, nab-paclitaxel has been approved in combination with 1) atezolizumab (PD-L1 inhibitor) for treatment of PD-L1 positive unresectable locally advanced or metastatic TNBC [Kang, C. and Syed, Y. Y. 2020]; 2) pembrolizumab for treatment of locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 with CPS ≥10 [U.S. Prescribing Information 2020].

The starting dose of chemotherapy in Arm 4: 100 mg/m^2 nab-paclitaxel, administered by IV infusion administered on a 3-week on (Days 1, 8 and 15)/1-week off schedule every 28 days, represent the standard of care per the approved product labels.

If the mTPI design calls for a de-escalation, the doses of pemetrexed and carboplatin, and nab-paclitaxel will be reduced as outlined in Table 3.

Table 3 Chemotherapy Dose Level Definitions

	Dose Level 0	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Carboplatin	AUC 5 mg/mL/min Maximum dose 750 mg	AUC 3.75 mg/mL/min Maximum dose 562.5 mg	AUC 2.5 mg/mL/min Maximum dose 375 mg	Discontinue treatment
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue treatment
Nab-paclitaxel	100 mg/m^2	80 mg/m^2	64 mg/m^2	Discontinue treatment
AUC=area under the curve				

Dose levels of pemetrexed, carboplatin and nab-paclitaxel below Dose Level -2 will not be explored. If the mTPI design calls for an additional de-escalation, enrollment into Arm 3 and/or Arm 4 will be closed. Arms 3 and/or 4 may stop early if the number of DLTs exceeds an acceptable rate while at the lowest possible dose combination

5.5.6 Dose Finding Using a Modified Toxicity Probability Interval Design

During dose escalation and confirmation, an mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be applied to identify a preliminary RP2D of MK-5890 when used as monotherapy (Arm 1) and in combination with pembrolizumab (Arm 2) according to the rules outlined in Table 4.

Six pre-determined dose levels of MK-5890 will be explored independently in each arm: 2 mg, 7 mg, 20 mg, 70 mg, 200 mg and 700 mg. It may be acceptable to de-escalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. All dose escalation decisions will be based on the occurrence of DLTs and will be made jointly by the investigators and the Sponsor. The dose of

pembrolizumab in Arm 2 will remain constant at 200 mg. Study treatment will be administered Q3W. There will be no intraparticipant dose escalation for participants enrolled in this study except as described in Section 7.2.3.

Treatment will be allocated by non-random assignment. Enrollment into the MK-5890 + pembrolizumab combination treatment arm (Arm 2) will begin once all participants at the second dose level in the MK-5890 monotherapy arm (Arm 1) complete the DLT evaluation period and a dose escalation decision has been made. This ensures that the starting dose of MK-5890 in the combination arm will be at least 2 levels below the dose being tested in the MK-5890 monotherapy arm. When both treatment arms are open for enrollment, IVRS/IWRS will alternate participant assignment between Arms 1 and 2 starting with Arm 1. For example, once the 20 mg dose cohort of Arm 1 (MK-5890 monotherapy) and the 2 mg dose cohort of Arm 2 (MK-5890 + pembrolizumab) are open for enrollment, the first participant will be allocated to Arm 1, the second participant will be allocated to Arm 2, the third participant will be allocated to Arm 1, etc. An observation period of at least 24 hours will occur between treatment initiation in the first 3 participants enrolled within each dose level. Each new dose cohort will open for enrollment without delay once the 21-day DLT evaluation period of the previous dose cohort is completed and a dose escalation decision is made.

In Table 4, the columns indicate the number of participants evaluable for DLT at the current dose, and the rows indicate the number of participants with at least one DLT. The entries of the table are the dose-finding decisions: escalate to the next higher dose (E), stay at the current dose (S), de-escalate to the next lower dose (D), and de-escalate to a lower dose and never test this dose again (ie, unacceptably toxic dose; [DU]).

A minimum of 3 participants are required at each dose. Depending on the accrual rate and the occurrence of DLTs, 3, 4, 5, or 6 participants may be enrolled within 21 days at each new dose. For example, if 0 out of 3 participants at a given dose level develops a DLT, then the dose can escalate to the next level. If 1 out of 3 participants at a given dose level develops a DLT, then additional participants should be enrolled at that dose level following the rules below. If 2 participants out of 3 develop a DLT, the dose will be de-escalated to the next lower dose level. If 3 out of 3 participants develop a DLT, the dose should be de-escalated and the current dose will not be explored further.

When adding participants to a dose level in response to a “stay” decision, the number of additional participants to be enrolled is capped to minimize exposure to a dose that may be unacceptably toxic (denoted as DU in Table 4). To determine how many more participants can be enrolled at the dose level, one can count steps in a diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants has experienced a DLT at a given dose level, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4 out of 6 participants). The same principles will be applied whether 3, 4, 5, or 6 participants are initially enrolled at a dose level.

A dose-finding decision of D or DU at the lowest dose level will stop the study. An E decision at the highest dose level will result in staying at that level.

Dose finding will end after 14 participants have been enrolled at any of the tested doses (including intermediate doses). The dose of MK-5890 in the combination arm (Arm 2) may not be escalated to a dose that is higher than the MK-5890 dose in the MK-5890 monotherapy arm (Arm 1), however, once dose escalation of MK-5890 in Arm 1 is stopped, the dose of MK-5890 in Arm 2 may be escalated up to that dose.

The pool-adjacent-violators-algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses in each treatment arm. The dose with an estimated DLT rate closest to 30% will be treated as a preliminary RP2D, however, the totality of the data will be considered before deciding on the dose(s) to carry forward to the expansion phase, and the escalation schedule may be adjusted based on PD, PK, and safety data emerging throughout the study. The preliminary RP2D of MK-5890 in the combination arm (Arm 2) will not exceed, but may equal, the preliminary RP2D in the MK-5890 monotherapy arm (Arm 1).

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 4, the observed rates of participants with DLTs at the RP2Ds may be slightly above or below 30%.

Table 4 Dose-Finding Rules per the Modified Toxicity Probability Interval Design

Number of Participants with at Least 1 DLT	**Number of Participants Evaluable for DLT at Current Dose**											
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

E=Escalate to the next higher dose
S=Stay at the current dose
D=De-escalate to the next lower dose
DLT=dose-limiting toxicity
DU=The current dose is unacceptably toxic
Target toxicity rate = 30%
Flat non-informative prior Beta (1,1) is used as a prior and $\varepsilon1=\varepsilon2=0.03$ [Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013]

In addition to testing MK-5890 as monotherapy and combination treatment with pembrolizumab in participants with advanced solid tumors, the dose escalation and confirmation phase will also include a cohort of participants with nonsquamous NSCLC who will be treated with 30 mg MK-5890 in combination with 200 mg pembrolizumab, 500 mg/m^2 pemetrexed, and AUC 5 mg/mL/min carboplatin for up to 4 cycles followed by maintenance therapy with MK-5890, pembrolizumab, and pemetrexed (Arm 3). MK-5890 will be given for up to a total of 6 months. Pembrolizumab and pemetrexed will be given for up to a total of 35 cycles with the possibility of continuing pemetrexed during the follow-up phase of the study at the discretion of the investigator per standard of care. All treatments will be given by IV infusion Q3W. For participants who continue pemetrexed after 35 cycles, pemetrexed will not be considered a new anticancer therapy. Enrollment in Arm 3 will begin with 6 participants. In the event of unacceptable toxicity during the chemotherapy combination, the doses of chemotherapy will be de-escalated according to the rules outlined in the mTPI design (Table 4). The chemotherapy doses that will be tested are outlined in Table 3. Arm 3 may stop early if the number of DLTs exceeds an acceptable rate while at the lowest possible dose combination.

In Amendment 3, the dose expansion phase will also include a cohort of participants with locally recurrent inoperable TNBC not previously treated with chemotherapy and which cannot be treated with curative intent or with not previously treated metastatic TNBC whose tumor PD-L1 CPS is less than 10 who will be treated with 30 mg MK-5890 in combination with 400 mg pembrolizumab (Q6W), 100 mg/m^2 nab-paclitaxel, administered by IV infusion administered on a 3-week on (Days 1, 8 and 15)/1-week off schedule every 28 days. MK-5890 and pembrolizumab will be given for up to a total of 18 cycles. Enrollment in Arm 4 will begin with 10 participants. In the event of unacceptable toxicity during the chemotherapy combination, the doses of chemotherapy will be de-escalated according to the rules outlined in the mTPI design (Table 4). The chemotherapy doses that will be tested are outlined in Table 3. Arm 4 may stop early if the number of DLTs exceeds an acceptable rate while at the lowest possible dose combination.

Dose finding will end after 10 participants have been treated at a dose level of the chemotherapy combination as long as the decision based on Table 4 is to stay or escalate. The doses of chemotherapy may not be de-escalated to doses lower than the lowest doses outlined in Table 3. If the mTPI design calls for a de-escalation beyond the lowest doses in Table 3, enrollment into Arm 3 will be closed.

5.5.7 CCI

CCI

[redacted]

6. STUDY POPULATION

Male and female participants with advanced solid tumors who are at least 18 years of age on the day of signing consent will be enrolled in this study.

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

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

1. a) Dose Escalation/Confirmation Phase (Arms 1 and 2): Have a histologically or cytologically confirmed advanced/metastatic solid tumor by pathology report and have received or been intolerant to all treatment known to confer clinical benefit.

   b) Dose Escalation/Confirmation Phase (Arm 3): Have a histologically or cytologically confirmed diagnosis of stage IV (M1a or M1b per current AJCC criteria, edition 8) nonsquamous NSCLC.

   Note: Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the participant is ineligible.

   Participants may be untreated or could have received and progressed on 1 prior regimen.

   Participants who have epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutant tumors should have received an approved targeted therapy.

   c) Dose Expansion Phase (Arm 2a): Have a diagnosis of TNBC. Participants must have received or been intolerant to not more than 2 lines of therapy for metastatic disease known to confer clinical benefit. Prior therapy should have included anthracycline and/or taxane for early-stage or metastatic disease. Participants must have lactate dehydrogenase (LDH) ≤2 x ULN at screening. Enrollment will be capped at a maximum of 7-10 participants who are PD-1/PD-L1 inhibitor treatment-refractory*.

   d) Dose Expansion Phase (Arm 1a, 2b, and 2c): Have a diagnosis of endometrial cancer. Participants must have received or been intolerant to no more than 2 prior lines of treatment known to confer clinical benefit. Prior therapy should have included platinum-containing regimens for early-stage or metastatic disease. Enrollment will be capped at a maximum of 5-7 participants per treatment arm who are PD-1/PD-L1 inhibitor treatment-refractory*.

*Participants will be considered to have PD-1/PD-L1 inhibitor treatment-refractory disease if they meet all of the following criteria:

i. Have received at least 2 doses of anti-PD-1/PD-L1 mAb at a local regulatory agency-approved dose and schedule.

ii. Have progressive disease after anti-PD-1/PD-L1 mAb defined according to RECIST 1.1. The initial evidence of progressive disease is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid clinical progression. Note: This determination is made by the investigator. If progressive disease is confirmed, the initial date of progressive disease documentation will be considered the date of disease progression.

iii. Have documented disease progression within 12 weeks of the last dose of anti-PD-1/PD-L1 mAb. Participants who were re-treated with anti-PD-1/PD-L1 mAb and participants who were on maintenance with anti-PD-1/PD-L1 mAb will not be considered to have PD-1/PD-L1 inhibitor treatment-refractory disease if more than 12 weeks elapse between disease progression and the last treatment date (with anti-PD1/PD-L1 therapy).

e) Dose Expansion Phase (Arm 4): Have TNBC with tumor PD-L1 CPS<10** that is either locally recurrent, inoperable, not previously treated with chemotherapy, and which cannot be treated with curative intent or metastatic disease not previously treated with chemotherapy.

Note: Participants with a history of locally recurrent TNBC, which was previously treated with curative intent, may be eligible.

i. TNBC, as defined by the most recent ASCO/CAP guidelines. Note: Participants initially diagnosed with hormone receptor–positive and/or HER2-positive breast cancer must have TNBC in a tumor biopsy obtained from a local recurrence or distant metastasis site.

ii. Have completed treatment for Stage I-III breast cancer, if indicated, and ≥6 months elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.

Note: Adjuvant radiation therapy is not considered treatment with curative intent for the purpose of calculating the ≥6-month interval requirement described above.

Note: First documentation of local or distant disease recurrence must be in the form of a dated biopsy, pathology, or imaging study report. A laboratory report indicating tumor marker elevation cannot be used as documentation of local or distant disease recurrence, unless accompanied by dated biopsy, pathology, or imaging study report.

Note: Participants who received taxane agents in the (neo)adjuvant setting can be treated with same class of chemotherapy (taxane), if ≥12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.

iii. Have been treated with (neo)adjuvant anthracycline, if they received systemic treatment in the (neo)adjuvant setting, unless anthracycline was contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician.

Note: Participants presenting with de novo metastatic TNBC are eligible for the study, if anthracycline is contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician.

**To calculate PD-L1 CPS, the PD-L1 IHC 22C3 pharmDx assay is required for PD-L1 testing. Tissue samples may be tested locally to determine eligibility. If local testing is used, each site investigator must ensure that PD-L1 testing is compliant with local regulations for guiding participant treatment decisions, notably that the PD-L1 IHC 22C3 pharmDx test kit is used in accordance with instructions on the label.

Tissue samples will also be sent for central testing although participants can enter the study based on local PD-L1 IHC 22C3 pharmDx test results.

When PD-L1 IHC 22C3 pharmDx testing cannot be performed locally, central testing must be performed to determine eligibility.

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

3. Have adequate organ function as defined in Table 5. Specimens must be collected within 7 days before the first dose of study treatment.

Table 5 Adequate Organ Function Laboratory Values

System / Parameter	Laboratory Value
HEMATOLOGICAL	
Absolute neutrophil count (ANC)	>1500/μL
Platelet count	>100 000/μL
Hemoglobin[1]	≥9 g/dL or ≥5.6 mmol/L without transfusions within 2 weeks of treatment initiation
RENAL	
Creatinine **OR** Measured or calculated creatinine clearance (CrCl)[2] NOTE: Glomerular filtration rate (GFR) can be used in place of CrCl	Creatinine ≤1.5 × institutional upper limit of normal (ULN) **OR** CrCl (GFR) ≥50 mL/min for participants with creatinine levels >1.5 × institutional ULN
HEPATIC	
Total bilirubin **OR** Direct bilirubin	Total bilirubin ≤1.5 × ULN **OR** Direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
Alanine aminotransferase (ALT) or serum glutamic-pyruvic transaminase (SGPT) **AND** Aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase (SGOT)	≤2.5 × ULN **OR** ≤5 × ULN for participants with liver metastases
COAGULATION	
International Normalized Ratio (INR) or Prothrombin time (PT)	≤1.5 × ULN unless the participant is receiving anticoagulant therapy
Activated partial thromboplastin time (aPTT) or Partial thromboplastin time (PTT)	≤1.5 × ULN unless the participant is receiving anticoagulant therapy

[1] Criteria must be met without packed red blood cell (pRBC) transfusion within last 2 weeks. Participants can be on a stable dose of erythropoietin (≥ approximately 3 months).
[2] Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Demographics

4. Be male or non-pregnant and non-breastfeeding female, ≥18 years of age on the day of signing informed consent.

5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Male participants:

6. 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 MK-5890 or pembrolizumab OR 180 days after the last dose of chemotherapeutic agents and refrain from donating sperm during this period.

Female participants:

7. 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.) She is not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b.) She is 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 MK-5890 or pembrolizumab OR 180 days after the last dose of chemotherapeutic agents.

Informed Consent

8. The participant (or legally acceptable representative if applicable) provides documented informed consent/assent for the study. The participant may also provide consent/assent for Future Biomedical Research; however, he/she may participate in the study without participating in Future Biomedical Research.

Other Study-Specific Criteria

9. Submit an evaluable baseline tumor sample for analysis (either a newly obtained or archival tumor sample). Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Details pertaining to tumor tissue submission can be found in the Procedures Manual.

6.2 Exclusion Criteria

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

Medical Conditions

1. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years.

   Note: The time requirement does not apply to the disease under study, participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, or other in situ cancers.

2. Has clinically active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously-treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic

(without evidence of progression by magnetic resonance imaging [MRI] scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks before the start of study treatment, and are off immunosuppressive doses of systemic steroids for at least 2 weeks prior to enrollment.

3. Has had a severe hypersensitivity reaction to treatment with a mAb and/or other components of the study treatment.

4. Has an active infection requiring systemic treatment.

5. Has a history of interstitial lung disease.

6. Has a history of (noninfectious) pneumonitis that required steroids or current pneumonitis.

7. Has symptomatic ascites or pleural effusion. Participants who are clinically stable after treatment of these conditions (including therapeutic thoracocentesis or paracentesis) will not be excluded from participation in this study.

8. Has previously had a stem cell or bone marrow transplant.

9. Has previously had a solid organ transplant.

10. 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.

11. Has known human immunodeficiency virus ([HIV]; HIV 1 or 2 antibodies) and/or active and acute Hepatitis B or C infections (eg, positive for HBsAg/HBV DNA or HCV RNA).

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, make administration of the study treatments 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 not fully recovered from any effects of major surgery without significant detectable infection. Surgeries that required general anesthesia must be completed at least 2 weeks before the start of study treatment. Surgeries that required regional/epidural anesthesia must be completed at least 72 hours before the first dose of study treatment and participants should be recovered.

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

15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

16. A WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. In such cases, the participant must be excluded from participation if the serum pregnancy test result is positive. Note, in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for the participant to start receiving study treatment.

Prior/Concomitant Therapy

17. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) before the first dose of study treatment, or has not recovered to CTCAE Grade ≤1 or better from any AEs that were due to cancer therapeutics administered more than 4 weeks earlier (this includes participants with previous immunomodulatory therapy with residual immune-related AEs [irAEs]). Participants receiving ongoing replacement hormone therapy for endocrine irAEs will not be excluded from participation in this study.

18. Is expected to require any other form of antineoplastic therapy while participating in this study.

19. Has received prior therapy with an agent directed to another stimulatory T cell receptor (eg, CD27, OX-40, CD137).

20. Is on chronic systemic steroid therapy in excess of replacement doses (eg, exceeding 10 mg/day of prednisone equivalent), or on any other form of immunosuppressive medication. Participants with reactive airway disease that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded from this study.

21. Is a regular user (including “recreational use”) of any illicit drugs at the time of signing informed consent, or has a recent history (within the last year) of substance abuse (including alcohol), as determined by the treating investigator. Participants who use cannabis for medicinal purposes or to treat specific symptoms will not be excluded unless it is being abused in the opinion of the treating investigator.

22. Has received a live-virus vaccine within 28 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal flu vaccines that do not contain live viruses are permitted. Intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not permitted.

Prior/Concurrent Clinical Study Experience

23. Is currently participating and receiving study therapy in a study of an investigational agent or has participated and received study therapy in a study of an investigational agent or has used an investigational device within 28 days before the first dose of study treatment.

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

Additional Exclusion Criteria for Participants Treated in Arm 3:

24. Has received radiation therapy to the lung that is >30 Gy within 6 months before the first dose of study treatment.

25. Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).

26. Is unable or unwilling to take folic acid or vitamin B12 supplementation.

Additional Exclusion Criteria for Participants Treated in Arm 4:

27. Has a known history of hypersensitivity or allergy to nab-paclitaxel or any of its components.

28. Has neuropathy ≥Grade 2.

29. Has a history of class II-IV congestive heart failure or myocardial infarction within 6 months of randomization.

30. Has received previous treatment with immune checkpoint inhibitor(s) (eg, PD-1/PD-L1)

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

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

6.3.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no restrictions on consumption of caffeine, alcohol, or tobacco.

6.3.3 Activity

There are no restrictions on activity.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the data entry guidelines.

6.5 Participant Replacement Strategy

In order to adequately evaluate the safety of the doses of study treatment administered in this study, all participants enrolled in the dose escalation and confirmation phase and Arm 4 in the expansion phase must meet the criteria for DLT evaluability in DLT evaluation period (see also Section 7.2.2). Participants are considered nonevaluable and will be replaced if:

- They are allocated but not treated;
- They discontinue from the study prior to completing all the safety evaluations in DLT evaluation period for reasons other than treatment-related AEs; and/or
- They receive less than 75% of any of the study drugs in Cycle 1 (eg, because the infusion had to be discontinued due to an infusion reaction) and do not experience a DLT.

Participants who are not evaluable will be replaced unless accrual to the cohort has stopped. Nonevaluable participants will not be counted toward the total number of participants in the cohort for DLT evaluation.

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

7.1 Treatments Administered

The study treatment(s) to be used in this study are outlined below in Table 6.

All study treatments will be administered on an out-patient basis.

Table 6 Study Treatments

Study Treatment Name:	MK-5890 (Arms 1, 2, 3, 1a, 2a, 2b, 2c, and 4)	Pembrolizumab (MK-3475; [Arms 2, 3, 2a, 2b, 2c and 4])	Pemetrexed (Arm 3)	Carboplatin (Arm 3)	Nab-paclitaxel (Arm 4)
Dose Formulation:	Solution for infusion	Solution for infusion	Lyophilized powder for injection	Solution for infusion	Lyophilized powder for injection
Unit Dose Strength(s):	50 mg/mL, 1.0 mL vial	25 mg/mL, 4.0 mL vial	500 mg	10 mg/mL, 60 mL vial	100 mg
Dose Level(s):	Arms 1 and 2: Escalating doses based on pre-specified dose-limiting toxicity (DLT) criteria once every 3 weeks Arms 3, 1a, 2a, 2b: 30 mg once every 3 weeks Arms 2c and 4: 30 mg once every 6 weeks	Arms 2, 3, 2a, and 2b: 200 mg once every 3 weeks Arms 2c and 4: 400 mg once every 6 weeks	500 mg/m^2 once every 3 weeks	AUC 5 mg/mL/min once every 3 weeks	100 mg/m^2
Route of Administration:	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Locally sourced	Locally sourced	Provided centrally by the Sponsor or locally sourced
IMP/NIMP:	IMP	IMP	IMP	IMP	IMP

AUC=area under the curve; IMP=investigational medicinal product; IV=intravenous; NIMP=non-investigational medicinal product

All supplies indicated in Table 6 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 (Escalation/Titration/Other)

7.2.1 Dose Administration/Escalation

7.2.1.1 CCI

CCI

CCI

[redacted]

7.2.2 Definition of Dose-limiting Toxicity

All toxicities will be graded using the NCI CTCAE, version 4.0 or later based on investigator assessment.

The DLT evaluation period of observation will be during Cycle 1 (21 days for Arm 1 to Arm 3).

In Arm 4, the DLT evaluation period will be during Cycle 1 of nab-paclitaxel (28 days).

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 administration, excluding toxicities clearly not related to study treatment, such as disease progression, environmental factors, unrelated trauma, etc.

1. Any Grade 4 nonhematologic toxicity (not laboratory).

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

    - Grade 4 thrombocytopenia of any duration;

    - Grade 3 thrombocytopenia associated with bleeding that requires a platelet transfusion.

3. Any nonhematologic AE Grade ≥3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.

4. Any Grade 3 or Grade 4 non-hematologic laboratory abnormality if:

    - Clinically significant medical intervention is required to treat the participant;

    - The abnormality leads to hospitalization;

    - The abnormality persists for >1 week;

    - The abnormality results in a drug-induced liver injury (DILI) (see Sections 9.3.1 and 9.3.7 for criteria).

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

5. Grade 3 or Grade 4 febrile neutropenia:

   - Grade 3 is defined as absolute neutrophil count (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 degrees F) for more than 1 hour.

   - Grade 4 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 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.

7. Any treatment-related toxicity that causes the participant to discontinue study treatment during Cycle 1.

8. Missing >25% of any study drug during the DLT evaluation period as a result of a drug-related AE(s).

9. Any Grade 5 toxicity.

If a participant experiences a DLT in DLT evaluation period study treatment may be discontinued following discussion between the Sponsor and the investigator. If the participant is deriving clinical benefit from the study treatment, the participant may be allowed to continue after discussion between the Sponsor and the investigator.

7.2.3 Cross-Over Treatment Phase (Optional)

Participants in the dose escalation and confirmation and dose expansion phases of the study with disease progression following treatment with MK-5890 in the monotherapy arms (Arm 1 and Arm 1a, respectively) may be eligible to participate in the cross-over treatment phase of this study. Participants who permanently discontinue MK-5890 monotherapy due to an AE, withdrawal of consent, or for any reason other than disease progression are not eligible for cross-over. Cross-over is optional, is at the discretion of the investigator, and requires the Sponsor's approval.

Disease progression must be assessed by imaging study using RECIST 1.1. Imaging must be completed to establish a new baseline for the cross-over phase.

Additional eligibility criteria for cross-over include:

- Participants must have adequate organ function as indicated by the laboratory values in Table 5;

- Participants must have no evidence of new or enlarging brain metastases; and
- Participants must have an ECOG performance status of 0 or 1.

If cross-over is being considered, the participant must be re-consented and the risks and benefits of continuing study treatment after disease progression should be reviewed prior to performing any cross-over-related procedures.

Although intraparticipant dose escalation is not allowed, at cross-over, participants in the dose escalation and confirmation phase may be eligible to receive the highest dose of MK-5890 that has passed the DLT evaluation period in the MK-5890 + pembrolizumab combination treatment arm at the time of cross-over. If that dose is higher than the MK-5890 dose the participant was receiving in the monotherapy arm, the increase in dose will be allowed only if the participant did not experience any drug-related AEs at the dose of MK-5890 the participant was receiving in the monotherapy arm. If that dose is lower than the MK-5890 dose the participant was receiving in the monotherapy arm, the MK-5890 dose the participant will receive in the combination treatment arm after cross-over will be de-escalated to the highest dose of MK-5890 that has passed an initial DLT evaluation period in the MK-5890 + pembrolizumab combination treatment arm. Participants who cross over to the MK-5890 + pembrolizumab combination treatment arm will not be counted toward the total number of participants in the cohort for DLT evaluation.

Participants in the dose expansion phase who cross over will receive 30 mg MK-5890.

The first dose of study treatment in the MK-5890 + pembrolizumab combination treatment arm should be administered no earlier than 21 days (3 weeks) and no later than 42 days (6 weeks) from the last dose of MK-5890 in the monotherapy arm unless otherwise discussed with the Sponsor.

Participants who cross over may receive up to 35 cycles of study treatment in the combination treatment arm after cross-over. Treatment duration after cross-over will not include the treatment duration in the monotherapy arm prior to cross-over.

The study procedures to be completed in the cross-over treatment phase and their timing are summarized in Section 2.8 (Schedule of Activities for the Cross-Over Treatment Phase). Safety and efficacy data from participants who cross over into the combination arm will be presented separately and will include all events starting from the date of the first dose of combination study treatment.

7.2.4 Timing of Dose Administration

Study treatment in Arms 1, 2, 3, 1a, 2a, and 2b will be administered by IV infusion Q3W. Study treatment in Arm 2c will be administered by IV infusion Q6W. MK-5890 will be administered over a period of approximately 90 minutes in all treatment arms. Based on preliminary safety information from the ongoing study, the Sponsor recommends that all participants treated with MK-5890 be prophylactically premedicated, 1.5 hours (±30 minutes) before infusion of MK-5890; see Section 7.2.5.3 for details.

In Arms 2, 3, 2a, 2b, and 2c, MK-5890 will be administered approximately 30 minutes after completion of the pembrolizumab infusion.

The order of infusions in Arm 3 will be as follows: pembrolizumab, MK-5890, pemetrexed, then carboplatin. Participants should receive premedication per the approved product labels for pemetrexed and carboplatin.

The order of infusions in Arm 4 will be as follows: pembrolizumab, MK-5890, then nab-paclitaxel. Participants should receive premedication for nab-paclitaxel per the approved product labels.

Every effort should be made to begin the first dose of study treatment as close as possible to the day of treatment allocation. All study treatments should be initiated after all pre-dose study procedures and assessments have been completed as detailed in Section 2.

In Arms 1 and 2, treatment in Cycle 2 may be administered up to 3 days after the scheduled Day 1, if necessary for administrative/logistical reasons. Beginning in Cycle 3, treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle. In Arm 3, treatment in Cycles 2-4 may be administered up to 3 days after the scheduled Day 1. Beginning in Cycle 5, treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle. In Arms 1a, 2a, 2b, and 2c and in participants who cross over to MK-5890 + pembrolizumab, treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle as of Cycle 2.

In addition, dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment (eg, elective surgery, unrelated medical events, participant vacations, and/or holidays). Participants should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor.

The reason for any variability in administration of study treatment outside of the protocol-specified window should be documented in the participant's chart and recorded on the electronic Case Report Form (eCRF).

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

7.2.5.1 Dose Modification and Toxicity Management for Adverse Events Associated With MK-5890 and/or Pembrolizumab

Adverse events (both nonserious and serious) associated with MK-5890 and pembrolizumab exposure may represent an immunologic etiology. These AEs may occur anywhere from shortly after the first dose to several months after the last dose of treatment.

The NCI CTCAE, version 4.0 or later must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-5890 alone, to pembrolizumab alone, or to the combination, and modify the dose as appropriate. If a dose modification for toxicity

occurs with MK-5890, the dose may not be re-escalated to the dose that preceded the dose modification. Dose modifications are always based on the previous cycle.

Reduction or holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study treatments. For example, in the MK-5890 + pembrolizumab combination arms (Arms 2, 3, 2a, 2b, and 2c), if MK-5890 is held due to an AE attributed to that treatment, then pembrolizumab may continue to be administered. The investigator must appropriately document the attribution of the AE. If, in the opinion of the investigator, the toxicity is related to the combination of the 2 agents, then both treatments should be held according to recommended dose modifications.

Participants may have up to 2 dose modifications of MK-5890 throughout the course of the study, as described in Table 7. If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from study treatment. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommendation should be followed (ie, dose reduction appropriate to the most severe toxicity).

Dose modification and treatment discontinuation guidelines for AEs related to MK-5890 are outlined in Table 7. The Sponsor may consider exceptions to the dose modification guidelines, after consultation.

Pembrolizumab treatment interruption/discontinuation and toxicity management guidelines are described in Section 7.2.5.2 and treatment guidelines associated with infusion-related reactions are described in Section 7.2.5.3.

Table 7 MK-5890 Dose Modification and Treatment Discontinuation Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Hematological toxicities:				
• Any Grade 1 hematological toxicity	No	N/A	N/A	N/A
• Any Grade 2 hematological toxicity, or Grade 3 toxicity that persists for ≤5 days	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves to baseline or Grade 1	Per medical assessment of the investigator; may decrease dose by 1 dose level	If AE persists for 12 weeks without resolution following reduction in dose
• Any Grade 3 hematologic toxicity that persists for >5 days, or Grade 4 hematological toxicity; or • Febrile neutropenia; or • Grade 3 thrombocytopenia of any duration if associated with bleeding	Yes	Treatment may be restarted when AE resolves to baseline or Grade 1	Decrease dose by 1 dose level	If AE persists for 12 weeks without resolution following reduction in dose Permanent study treatment discontinuation should be considered for any severe or life-threatening event
Nonhematological toxicities:				
• Any Grade 1 nonhematological toxicity; or • Grade 2 alopecia; or • Grade 2 fatigue	No	N/A	N/A	N/A
• Any Grade 2 nonhematological toxicity except Grade 2 alopecia and Grade 2 fatigue	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves to baseline or Grade 1	Per medical assessment of the investigator; may decrease dose by 1 dose level	If AE persists for 12 weeks without resolution following reduction in dose
• Any Grade 3 or Grade 4 nonhematological toxicity (not including laboratory abnormalities, unless clinically significant medical intervention is required, the abnormality leads to hospitalization, or the abnormality persists for >1 week)	Yes	Treatment may be restarted when AE resolves to baseline or Grade 1	Decrease dose by 1 dose level	If AE persists for 12 weeks without resolution following reduction in dose Permanent study treatment discontinuation should be considered for any severe or life-threatening event

AE=adverse event; N/A=not applicable

In case toxicity does not resolve to Grade 0-1 within 12 weeks after the last dose of study treatment, MK-5890 should be discontinued after consultation with the Sponsor.

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

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

7.2.5.2 Dose Modification and Toxicity Management for Immune-Related AEs Associated With Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and/or 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 monotherapy, coformulations, or IO combinations are provided in Table 8.

Table 8 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• 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 [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

7.2.5.3 Toxicity Management of Infusion Reactions Related to Pembrolizumab and MK-5890

Pembrolizumab and MK-5890 may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of the infusion.

Based on preliminary safety information from the ongoing study, the Sponsor recommends that all participants treated with MK-5890 be prophylactically premedicated, 1.5 hours (±30 minutes) before infusion of MK-5890 with the following:

- Diphenhydramine 50 mg orally (or equivalent dose of antihistamine); and
- Acetaminophen 500-1000 mg orally (or equivalent dose of analgesic).

Corticosteroids may be added after consultation with the Sponsor.

Depending on the timing of premedication, these may be administered before pembrolizumab, if necessary.

Toxicity management guidelines for pembrolizumab-associated infusion reactions are provided in Table 9.

Table 9 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 therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤24 hours
	• **Stop infusion**
	• Additional appropriate medical therapy may include, but is not limited to:
	  • IV fluids
	  • Antihistamines
	  • NSAIDs
	  • Acetaminophen
	  • Narcotics
	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator
	• If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose
	• **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment**
		Participant may be premedicated 1.5 hours (±30 minutes) prior to infusion of pembrolizumab with:
		• Diphenhydramine 50 mg PO (or equivalent dose of antihistamine)
		• Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic)

Grade 3 or 4
Grade 3:
Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)
Grade 4:
Life-threatening; pressor or ventilatory support indicated
	• **Stop infusion**
	• Additional appropriate medical therapy may include, but is not limited to:
	  • Epinephrine**
	  • IV fluids
	  • Antihistamines
	  • NSAIDs
	  • Acetaminophen
	  • Narcotics
	  • Oxygen
	  • Pressors
	  • Corticosteroids
	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator
	• Hospitalization may be indicated
	• **In cases of anaphylaxis, epinephrine should be used immediately
	• **Participant is permanently discontinued from further study treatment**
		No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study treatment administration. For further information, please refer to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 at http://ctep.cancer.gov		

7.2.5.4 Dose Modification for Chemotherapy

Participants should receive premedication per the approved product labels for pemetrexed, carboplatin and nab-paclitaxel.

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 10 and Table 11. These serve only as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. Please refer to Table 3 for definitions of the dose levels.

Dose modifications for individual study treatment(s) must be based on the maximum toxicity experienced during the previous treatment period with this(these) drug(s) and must be performed in a stepwise manner, as described in Table 10 and Table 11. Toxicity (except for alopecia) needs to resolve to ≤Grade 1 or baseline prior to resuming treatment with the same drug(s). For participants requiring a study treatment dose modification, the next treatment period with this(these) drug(s) may be delayed, if the scheduled off-drug periods are not adequate to allow for recovery to ≤Grade 1 or the baseline status of the participant. If a dose reduction for toxicity occurs with chemotherapy, the dose(s) may not be re-escalated. Participants may have a maximum of 2 dose modifications per chemotherapy (if applicable) for toxicities throughout the course of the study. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity).

If the toxicity may be attributed to both an immunologic etiology (pembrolizumab-related) and chemotherapy, pembrolizumab should be interrupted or discontinued and chemotherapy should be reduced (if applicable), interrupted, or discontinued, according to local guidelines and practices. Participants may have chemotherapy discontinued and continue on pembrolizumab and MK-5890. Similarly, participants may discontinue pembrolizumab and/or MK-5890 and continue on chemotherapy, if appropriate. Chemotherapy administration may be interrupted due to AEs for a maximum of 4 weeks.

Use of colony-stimulating factors (CSFs) for primary prophylaxis is permitted at the investigator's discretion. Refer to the American Society of Clinical Oncology guidelines for use of CSFs [Smith, T. J., et al 2006].

Table 10 Recommended Dose Modifications for Chemotherapy-Related Hematological Toxicities

Platelets		ANC	Carboplatin	Pemetrexed
			Dose level from Table 3	
≥50,000/mcL	AND	≥500/mcL	DL 0	DL 0
≥50,000/mcL	AND	<500/mcL	DL -1	DL -1
<50,000/mcL without bleeding	AND	ANY	DL -1	DL -1
<50,000/mcL with Grade ≥2 bleeding	AND	ANY	DL -2	DL -2
ANY	AND	<1,000/mcL + fever ≥38.5°C (101°F)	DL -1	DL -1
DL=dose level				

Table 11 Recommended Dose Modifications for Chemotherapy-Related Non-Hematological Toxicities

Event	CTCAE Grade	Carboplatin	Pemetrexed
		Dose level from Table 3	
Nausea or vomiting	Grade 3or 4	DL 0	DL 0
Diarrhea	Grade 3or 4	DL 0	DL -1
Mucositis	Grade 3or 4	DL 0	DL -2
Neurotoxicity	Grade 2	DL 0	DL 0
	Grade 3or 4	DL -1	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1
	Grade 4	Discontinue treatment	Discontinue treatment
Other non-hematological toxicities	Grade 3or 4	DL -1	DL -1
CTCAE=Common Terminology Criteria for Adverse Events; DL=dose level			

Suggested dose modifications for nab-paclitaxel should follow local guidelines and practices.

Creatinine clearance (CrCl): CrCl will be based on the original weight-based Cockcroft-Gault Method or institutional standard. CrCl must be ≥45 mL/min prior to the administration of chemotherapy. Carboplatin and/or pemetrexed may be delayed for up to 42 days to allow the participant time to recover from the toxicity. If a participant's CrCl value has not returned to ≥45 mL/min within 42 days after the previous dose, carboplatin and/or pemetrexed must be discontinued.

7.2.5.5 Management Guidelines for Overlapping Toxicities

For overlapping toxicities where it is unclear if the event is related to one or a combination of drugs, it is recommended to hold all applicable drugs, and initiate management per MK-5890 Dose Modification and Treatment Discontinuation Guidelines for Drug-Related Adverse

Events (Table 7) for MK-5890 treatment and per Dose Interruption/Discontinuation and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab (Table 8) for pembrolizumab treatment. Table 10 and Table 11 or standard of care should be followed for management of toxicities deemed related to chemotherapy.

7.3 Method of Treatment Assignment

Treatment allocation will occur centrally using an IVRS/IWRS.

Participants in the dose escalation and confirmation phase of the study will be allocated by non-random assignment to 1 of 2 treatment arms: escalating doses of MK-5890 Q3W as monotherapy (Arm 1) or escalating doses of MK-5890 Q3W in combination with 200 mg pembrolizumab Q3W (Arm 2).

Enrollment into the MK-5890 + pembrolizumab combination treatment arm (Arm 2) will begin once all participants at the second dose level in the MK-5890 monotherapy arm (Arm 1) complete the DLT evaluation period and a dose escalation decision has been made. This ensures that the starting dose of MK-5890 in the combination arm will be at least 2 levels below the dose being tested in the MK-5890 monotherapy arm. When both treatment arms are open for enrollment, IVRS/IWRS will alternate participant assignment between Arms 1 and 2 starting with Arm 1. For example, once the 20 mg dose cohort of Arm 1 (MK-5890 monotherapy) and the 2 mg dose cohort of Arm 2 (MK-5890 + pembrolizumab) are open for enrollment, the first participant will be allocated to Arm 1, the second participant will be allocated to Arm 2, the third participant will be allocated to Arm 1, etc. An observation period of at least 24 hours will occur between treatment initiation in the first 3 participants enrolled within each dose level. Each new dose cohort will open for enrollment without delay once the 21-day DLT evaluation period of the previous dose cohort is completed and a dose escalation decision is made.

Participants with nonsquamous NSCLC enrolled as part of Amendment 02 will be allocated to combination treatment with 30 mg MK-5890, 200 mg pembrolizumab, 500 mg/m^2 pemetrexed, and AUC 5 mg/mL/min carboplatin, all given Q3W (Arm 3).

Participants in the dose expansion phase of the study with TNBC will be allocated to 30 mg MK-5890 Q3W in combination with 200 mg pembrolizumab Q3W (Arm 2a). Participants in the dose expansion phase of the study with endometrial will be allocated by random assignment at a 1:1:1 ratio to 30 mg MK-5890 Q3W as monotherapy (Arm 1a), 30 mg MK-5890 Q3W in combination with 200 mg pembrolizumab Q3W (Arm 2b), or 30 mg MK-5890 Q6W in combination with 400 mg pembrolizumab Q6W (Arm 2c).

In addition, participants with locally recurrent inoperable TNBC cancer not previously treated with chemotherapy and which cannot be treated with curative intent or with previously not treated metastatic TNBC whose tumor PD-L1 CPS is less than 10 (Arm 4) will be allocated to 30 mg MK-5890 in combination with 400 mg pembrolizumab and 100 mg/m^2 nab-paclitaxel; MK-5890 and pembrolizumab given Q6W for 18 cycles and nab-paclitaxel will be administered on a 3-week on (Days 1, 8 and 15)/1-week off schedule every 28 days.

7.3.1 Stratification

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

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 MK-5890 and pembrolizumab are provided in the Pharmacy Manual. Pemetrexed and carboplatin should be prepared and administered per their approved product labels.

The rationale for selection of doses to be used in this study is provided in Section 5.5 - Justification for Dose. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

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

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

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 during the study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. The decision to continue the participant on study treatment, however, requires the mutual agreement of the investigator, the Sponsor, and the participant.

7.7.1 Acceptable Concomitant Medication

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care except for those that are prohibited as described in Section 7.7.2. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after the 30-day post-study treatment period related to SAEs and ECIs as defined in Section 9.3 should be recorded.

7.7.2 Prohibited Concomitant Medications

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 and/or as pre/post-medication to prevent AEs associated with chemotherapy. 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.
- Phenytoin during treatment with carboplatin
- Participants taking NSAIDs or salicylates will not take the NSAID or salicylate (other than an aspirin dose ≤1.3 g per day) for 2 days before, the day of, and 2 days after receiving pemetrexed. Participants taking NSAIDs or salicylates with a long half-life (eg, naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAID or salicylates for 5 days before, the day of, and 2 days after pemetrexed.

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

7.7.3 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Section 7.2.5.2, Table 8. Toxicity management guidelines for infusion reactions related to pembrolizumab and MK-5890 are outlined in Section 7.2.5.3, Table 9. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to study treatment.

Note: If after evaluation of the event, it is determined not to be related to MK-5890 and/or pembrolizumab, the investigator does not need to follow the treatment guidance.

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

7.7.3.1 Antiemetic Use

For participants receiving chemotherapy, antiemetic therapy should follow MASCC; Section 12.9) or appropriate local guidelines and should, for the first 4 cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and aprepitant (or equivalent NK-1 receptor antagonist) as per the guideline followed.

7.7.3.2 Colony-Stimulating Factors

For participants receiving chemotherapy, the ASCO guidelines for use of CSFs, or local equivalent, should be used for patient management [Smith, T. J., et al 2006]. Use of CSFs for primary prophylaxis is permitted at the investigator's discretion.

7.7.3.3 Pemetrexed Premedication

All participants must receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis as listed below or per the local label:

- Folic acid, 350 μg to 1000 μg orally: At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, through the full course of therapy, and for 21 days after the last dose of pemetrexed.

- Vitamin B12, 1000 μg by IM injection: Vitamin B12 must be given in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

- Dexamethasone prophylaxis, 4 mg orally twice per day (or equivalent): Dexamethasone may be taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 through 4 but are not to exceed doses in MASCC guidelines (Section 12.9) or appropriate local guidelines.

7.7.3.4 Nab-paclitaxel Premedication

Premedication for nab-paclitaxel is determined according to local label.

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 (SoA) and Section 9.10.3 – Discontinued Participants Continuing to be Monitored in the 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 experiences confirmed radiographic disease progression as outlined in Section 9.2 (except if the Sponsor approves treatment continuation).
- The participant experiences unacceptable adverse experiences as described in Section 9.3.
- The participant experiences intercurrent illness that prevents further administration of study treatment.
- The participant has a medical condition or personal circumstance, which in the opinion of the investigator and/or the Sponsor, places the participant at unnecessary risk if study treatment administration is continued.
- The participant experiences recurrent Grade 2 pneumonitis.
- The participant experiences progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- The participant has a confirmed positive serum pregnancy test.
- The participant does not comply with study treatment or procedure requirements.

- The investigator decides to withdraw the participant.

- The participant completes study treatment (ie, Arms 1 and 1a: 35 cycles of MK-5890; Arm 2: 35 cycles of MK-5890/pembrolizumab; Arm 3: 6 months of MK-5890/35 cycles of pembrolizumab/35 cycles of pemetrexed [with the possibility of continuing during the follow-up phase of the study]/4 cycles of carboplatin; Arms 2a and 2b: 6 months of MK-5890/35 cycles of pembrolizumab; Arm 2c: 6 months of MK-5890/18 cycles of pembrolizumab; and Arm 4: 30 mg MK-5890 (Q6W) for up to 18 cycles in combination with 400 mg pembrolizumab (Q6W) for up to 18 cycles and 100 mg/m^2 nab-paclitaxel administered on a 3-week on (Days 1, 8 and 15)/1-week off schedule every 28 days).

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

Participants in the dose escalation and confirmation and dose expansion phases of the study who discontinue MK-5890 in the monotherapy arm due to disease progression may, at the investigator's discretion and after consultation with the Sponsor, cross-over to MK-5890 + pembrolizumab combination treatment as described in Section 7.2.3. The number of treatment cycles for cross-over participants will be calculated starting with the first dose of MK-5890 + pembrolizumab combination treatment.

If a participant experiences a DLT in DLT evaluation period, study treatment may be discontinued following discussion between the Sponsor and the investigator. If the participant is deriving clinical benefit from the study treatment, the participant may be allowed to continue after discussion between the Sponsor and the investigator.

If a participant initiates another anticancer therapy other than the assigned study treatment(s), the study treatment(s) should be discontinued and the participant will move into the survival follow-up phase. Note: For participants in Arm 3 who continue pemetrexed after 35 cycles, pemetrexed will not be considered a new anticancer therapy.

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 – Discontinuation and Withdrawal. 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 Procedures Manual.

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

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 documented 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

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

Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the disease for which the participant has enrolled in the study will be recorded separately and not listed as medical history.

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 starting the study. Treatment for the disease for which the participant has enrolled in the study will be recorded separately and not listed as a prior medication.

9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Post-Treatment Safety Follow-Up visit.

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

All new anticancer therapy initiated after the study start must be recorded on the eCRF.

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 treatment allocation. 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 9.10.1.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants in the study will be allocated to a study treatment 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

Administration of study treatment will be witnessed by the investigator and/or study staff.

The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

9.1.8.1 Timing of Dose Administration

All study treatments will be administered by IV infusion on an out-patient basis. In Arms 1 and 1a (MK-5890 monotherapy), Arms 2, 2a, and 2b (MK-5890 and pembrolizumab), and Arm 3 (MK-5890, pembrolizumab, pemetrexed, and carboplatin), study treatment will be administered Q3W, ie, on Day 1 of every 21-day cycle. In Arm 2c, MK-5890 and pembrolizumab will be administered Q6W, ie, on Day 1 of every 42-day cycle.

MK-5890 will be administered over a period of approximately 90 minutes in all treatment arms. Based on preliminary safety information from the ongoing study, the Sponsor recommends that all participants treated with MK-5890 be prophylactically premedicated, 1.5 hours (±30 minutes) before infusion of MK-5890; see Section 7.2.5.3 for details.

In Arms 2, 3, 2a, 2b, and 2c, pembrolizumab will be administered first, with administration of MK-5890 occurring approximately 30 minutes after completion of the pembrolizumab infusion.

The order of infusions in Arm 3 will be as follows: pembrolizumab, MK-5890, pemetrexed, then carboplatin. Participants should receive premedication per the approved product labels for pemetrexed and carboplatin.

The order of infusions in Arm 4 will be as follows: pembrolizumab, MK-5890, then nab-paclitaxel. Participants should receive premedication per the approved product labels for nab-paclitaxel.

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

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

9.1.10 Participant Blinding/Unblinding

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

9.1.11 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical study that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and 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.

Additional guidance regarding critical equipment (if applicable) is provided in the Procedures Manual, Pharmacy Manual, and Site Imaging Manual.

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

Tumor imaging should be acquired by computed tomography ([CT], strongly preferred). Magnetic resonance imaging should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality, ideally the same scanner, and use of contrast should be used in a participant throughout the study to optimize the visualization and reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. The schedule of disease assessment should not be adjusted for delays, if any, in cycle starts.

Response will be assessed by the investigator; however, scans used for tumor measurements may be requested for potential central review.

9.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days before the first dose of study treatment. Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within the timeframe defined in the SoA. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Participants with previously-treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT was used at prior imaging) for at least 4 weeks before the first dose of study treatment. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 28 days before starting the study as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

9.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed 9 weeks (±7 days) after the first dose of study treatment. 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, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, or death, whichever occurs first.

Per RECIST 1.1, objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm partial response (PR) or complete response (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 every 9 weeks, 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.

Per iRECIST [Seymour, L., et al 2017], disease progression should be confirmed by the site 4 to 8 weeks after the first radiologic evidence of progressive disease in clinically stable participants. Participants who have unconfirmed disease progression may continue on study 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

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

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks) to monitor disease status until disease progression, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, or death, whichever occurs first.

9.2.1.4 RECIST 1.1 Assessment of Disease

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

9.2.1.5 iRECIST 1.1 Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants

should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 7. This allowance to continue treatment despite initial radiologic progressive disease takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

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

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 progressive disease, and is not required to have repeat tumor imaging for confirmation of disease progression 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 disease progression by iRECIST, per investigator assessment.

If repeat imaging does not confirm disease progression 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 disease progression is confirmed, participants will be discontinued from study treatment.

If a participant has confirmed radiographic progression (iRECIST confirmed progressive disease [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 outlined in Section 2.

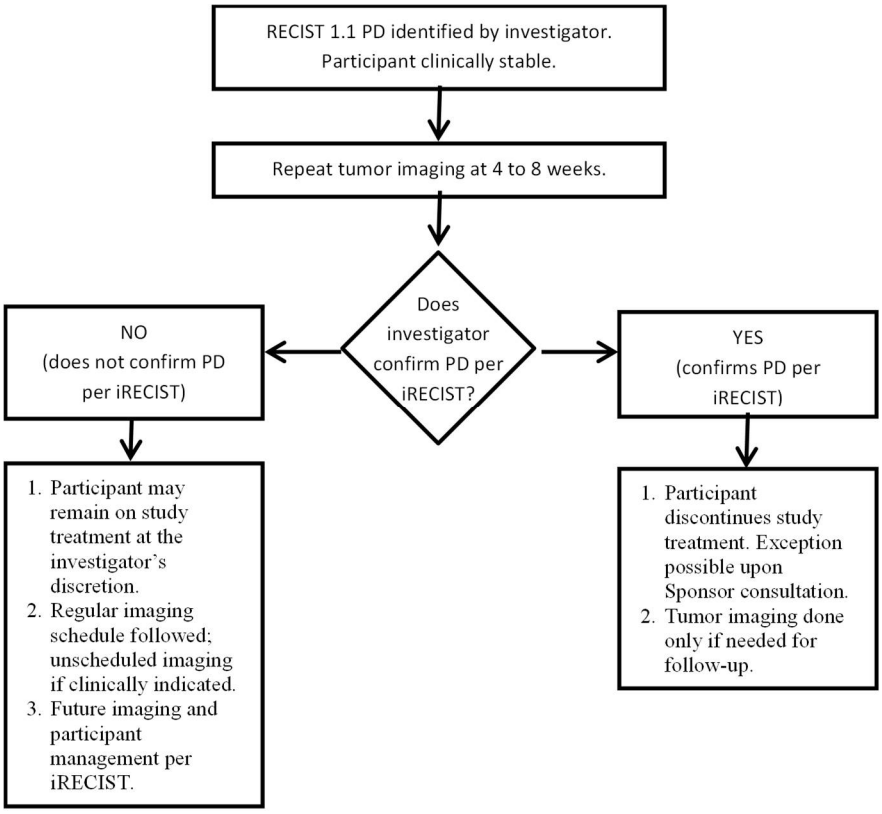
A description of the adaptations and iRECIST process is provided in Appendix 7, with additional details in the iRECIST publication. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in [Table 12] and illustrated as a flowchart in [Figure 3].

Table 12 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 per investigator assessment	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 iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD at the investigator's discretion ONLY	Discontinue study treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required	Discontinue study 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 at the investigator's discretion ONLY	Discontinue study 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 at the investigator's discretion. Next tumor image should occur according to the regular imaging schedule

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

Figure 3 Imaging and Treatment for Clinically Stable Participants After First Radiologic Evidence of Progressive Disease



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 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status as specified in the SoA.

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

The definitions of an adverse event (AE) and 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 unless it results in hospitalization or death as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

AEs, 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 AEs, 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 participant provides documented informed consent 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 causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of 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 MK-5890 or pembrolizumab OR 180 days after the last dose of chemotherapeutic agents, 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 13.

Table 13 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 AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and 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 AEs, SAEs, 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 treated 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 AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

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

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the 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

Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

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) 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 (ECIs)

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 MK-5890 by ≥20% of the indicated dose. An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. No specific information is available on the treatment of overdose of MK-5890 or pembrolizumab. In the event of overdose, MK-5890/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.

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

9.5.1 Physical Examinations

The investigator or qualified designee will perform a full physical examination at screening, Cycle 1, and at the End of Treatment visit. Directed physical examinations may be done at the other time points unless a full examination is deemed necessary.

Clinically significant abnormal findings at screening should be recorded as medical history. After the first dose of 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 sign measurements, which include temperature, pulse, respiratory rate, and blood pressure.

9.5.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. Additional ECGs at time points not specified in the SoA may be performed as clinically necessary.

Clinically significant abnormal findings before the first dose of study treatment should be recorded as medical history. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

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.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 5. At screening, these tests should be performed within 7 days before the first dose of study treatment. Pre-dose hematology and chemistry testing can be conducted up to 72 hours before the first dose of study treatment unless otherwise noted in Section 2. If screening tests are performed within 72 hours before the first dose of study treatment, they do not need to be repeated for the Cycle 1, Day 1 time point.

9.5.4.2 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy at screening and within

72 hours before the first dose of study treatment. Monthly testing should be conducted per local regulations. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from study treatment in the event of a positive or borderline-positive test result.

9.6 CCI

CCI

9.7 Pharmacodynamics

Venous blood samples of MK-5890 will be collected for measurement of receptor availability and soluble receptor analyses. Sample collection, storage, and shipment instructions for PD samples will be provided in the Laboratory Manual.

If deemed appropriate, the Sponsor may eliminate the need for PD sampling and testing.

9.8 CCI

CCI

CCI [redacted]

9.9 CCI [redacted]

CCI [redacted]

9.10 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.

9.10.1 Screening Period

During the screening period, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1 and Section 6.2. Screening procedures may be repeated after consultation with the Sponsor.

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

- Safety laboratory tests are to be performed within 7 days before the first dose of study treatment.
- For WOCBP, a urine or serum pregnancy test will be performed within 72 hours before the first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Newly obtained tumor tissue is defined as tissue collected within 90 days before the first dose of study treatment. Archival tumor tissue is defined as tissue collected greater than 90 days before the first dose of study treatment. The actual tumor sample is not required to be at the study site within the 28-day screening period.

9.10.2 Treatment Period

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.

9.10.3 Discontinued Participants Continuing to be Monitored in the Study

The End of Treatment visit should occur at the time study treatment is discontinued for any reason. Visit requirements are outlined in Section 2 - Schedule of Activities (SoA).

If the End of Treatment visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-Up visit, the End of Treatment visit procedures and any additional safety follow-up procedures should be performed.

Additional details regarding participant withdrawal and discontinuation are described in Section 8 - Discontinuation/Withdrawal Criteria.

9.10.3.1 Safety Follow-Up Visit

Participants will be required to return to the clinic for the Safety Follow-Up visit approximately 30 days after the last dose of study treatment or before initiating a new anticancer therapy, whichever occurs first. If the Safety Follow-Up visit occurs less than 30 days after the last dose of study treatment, a subsequent follow-up phone call should be made 30 days after the last dose of study treatment to determine if any AEs occurred since the last study visit.

After treatment discontinuation, participants will be monitored for AEs for 30 days and SAEs for 90 days (30 days if the participant initiates new anticancer therapy). Participants with an ongoing AE at the time of treatment discontinuation will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

9.10.3.2 Imaging Follow-Up Visits

Participants who discontinue study treatment for reasons other than confirmed disease progression will have post-treatment follow-up imaging every 9 weeks for disease status until disease progression, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, or death, whichever occurs first.

9.10.3.3 Survival Follow-Up Visits

Participants, who experience confirmed disease progression or initiate a new anticancer therapy will be contacted by telephone approximately every 12 weeks for survival until participant withdrawal of consent, becoming lost to follow-up, death, or the end of the study, whichever occurs first.

9.10.4 Survival Status

To ensure current and complete survival data is available, updated survival status may be requested during the course of the study by the Sponsor. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants who 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 non-confirmatory analyses will be outlined in a separate 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 non-confirmatory 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 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 study. Full details are in the Statistical Analysis Plan (SAP), Section 10.2 through to Section 10.12.

Study Design Overview	Phase 1 study of MK-5890 monotherapy, MK-5890 in combination with pembrolizumab in participants with advanced solid tumors, MK-5890 in combination with pembrolizumab, pemetrexed, and carboplatin in participants with nonsquamous NSCLC, and MK-5890 in combination with pembrolizumab and nab-paclitaxel in participants with locally recurrent inoperable TNBC not previously treated with chemotherapy and which cannot be treated with curative intent or with not previously treated metastatic TNBC whose tumor PD-L1 CPS is less than 10. The study applies a modified TPI design for dose escalation and confirmation of preliminary RPTDs, followed by an expansion phase with 3 efficacy cohorts (2 arms with TNBC and one arm with endometrial cancer).

Analysis Populations	Safety: All-Subjects-as-Treated (ASaT) PK: Per-Protocol (PP) Efficacy: Full Analysis Set (FAS)
Primary Endpoint(s)	Safety in participants treated with MK-5890 monotherapy and MK-5890 in combination with pembrolizumab: Number (proportion) of participants with DLT(s), AE(s), and who discontinue study treatment due to AE(s)
Secondary Endpoints	• PK parameters of MK-5890 when used as monotherapy, in combination with pembrolizumab, in combination with pembrolizumab, pemetrexed, and carboplatin, and in combination with pembrolizumab and nab-paclitaxel • ORR in participants treated with MK-5890 when used as monotherapy, in combination with pembrolizumab, in combination with pembrolizumab and nab-paclitaxel in the dose expansion phase of the study • Safety in participants treated with MK-5890 in combination with pembrolizumab, pemetrexed, and carboplatin: Number (proportion) of participants with DLT(s), AE(s), and who discontinue study treatment due to AE(s) • Safety in participants treated with MK-5890 in combination with pembrolizumab and nab-paclitaxel: Number (proportion) of participants with DLT(s), AE(s), and who discontinue study treatment due to AE(s)
Statistical Methods for Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	For the secondary endpoint of ORR as assessed by the investigator based on RECIST 1.1, the point estimate and 95% confidence interval (Clopper-Pearson interval) will be evaluated separately in participants in the dose expansion phase treated with MK-5890 as monotherapy (Arm 1a), MK-5890 in combination with pembrolizumab (Arms 2a, 2b, and 2c), MK-5890 in combination with pembrolizumab and nab-paclitaxel (Arm 4) using exact binomial distribution. Pairwise comparison will be conducted for ORR among Arm 1a (30 mg MK-5890 Q3W), Arm 2b (30 mg MK-5890 in combination with 200 mg pembrolizumab Q3W), and Arm 2c (30 mg MK-5890 in combination with 400 mg pembrolizumab Q6W) administered to participants with endometrial cancer using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The statistical methods for the tertiary/exploratory efficacy endpoints will be documented in a separate sSAP. PK parameters of study treatments will be summarized by planned visit and time for each dose separately.

Treatment Assignment	All participants will be allocated to treatment centrally through IVRS/IWRS. Participants in the dose escalation and confirmation phase will be allocated by non-random assignment to receive MK-5890 monotherapy (Arm 1) or MK-5890 in combination with pembrolizumab (Arm 2). Participants in the dose escalation and confirmation phase with nonsquamous NSCLC enrolled as part of Amendment 02 will be allocated to receive MK-5890 in combination with pembrolizumab, pemetrexed, and carboplatin (Arm 3). Participants in the dose expansion phase with TNBC will be allocated to receive 30 mg MK-5890 in combination with 200 mg pembrolizumab Q3W (Arm 2a). Participants in the dose expansion phase with endometrial cancer will be randomized at a 1:1:1 ratio to 30 mg MK-5890 Q3W (Arm 1a), 30 mg MK-5890 in combination with 200 mg pembrolizumab Q3W (Arm 2b), or 30 mg MK-5890 in combination with 400 mg pembrolizumab Q6W (Arm 2c). Participants in the dose expansion phase with TNBC enrolled as part of Amendment 03 will be allocated to 30 mg MK-5890 in combination with 400 mg pembrolizumab Q6W and 100 mg/m^2 nab-paclitaxel (Arm 4).
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. In the dose escalation and confirmation phase (Arm 1, Arm 2 and Arm 3) and the expansion phase (Arm 4), the pool-adjacent-violators algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at each tested dose level of MK-5890 and the 80% Bayesian credible intervals for the estimates will be provided.
Interim Analyses	In the dose escalation and confirmation phase (Arm 1, Arm 2 and Arm 3) and the expansion phase (Arm 4), data will be examined on a continuous basis to allow for dose-finding decisions using the mTPI design. In the dose expansion phase, the totality of the data will be examined once the first 15 participants with TNBC in Arm 2a are enrolled and have at least 1 post-baseline scan to decide whether or not to continue enrollment to 30 participants. In addition, the totality of the data will be examined once the first 10 participants with endometrial cancer per treatment arm are enrolled and have at least 1 post-baseline scan to decide whether or not to continue enrollment to 20 participants in that arm. The totality of the data will be examined once the first 20 participants with TNBC in Arm 4 are enrolled and have at least 1 post-baseline scan to decide whether or not to continue enrollment to 40 participants in that arm. Other interim analyses (eg, for efficacy) may be conducted to enable future study planning at the Sponsor's discretion.

Multiplicity	No multiplicity adjustment is planned in this Phase 1 study.
Sample Size and Power	During the dose escalation and confirmation phase, approximately 72 participants are expected to be enrolled (62 participants in Arms 1 and 2, and 10 participants in Arm 3). The actual sample size will depend on the safety profile of MK-5890 in each treatment arm but is expected to be in line with a typical Phase 1 first-in-human oncology study. In the dose expansion phase, approximately 130 participants are expected to be enrolled, including 30 participants with TNBC in Arm 2a, 60 participants with endometrial cancer (20 participants per arm) and 40 participants with TNBC in Arm 4. The actual sample size will depend on the safety profile of MK-5890 in combination with pembrolizumab and nab-paclitaxel (Arm 4) and efficacy profile in each arm. In total, approximately 202 participants will be used for study planning purposes.

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 study is open-label, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

10.3 Hypotheses/Estimation

Objectives of the study are outlined in Section 4 - Objectives/Hypotheses and Endpoints. No hypotheses are being tested in this study.

10.4 Analysis Endpoints

10.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

ORR as assessed by the investigator based on RECISIT 1.1 for participants treated with MK-5890 monotherapy, MK-5890 in combination with pembrolizumab, and MK-5890 in combination with pembrolizumab and nab-paclitaxel in the dose expansion phase is a secondary endpoint in this study. All other efficacy endpoints described in Section 4 are tertiary/exploratory endpoints. A description of efficacy measures is provided in Section 9.2 - Efficacy Assessments.

Objective response rate is defined as the proportion of participants who have achieved confirmed CR or PR.

Progression-free survival is defined as the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first.

Overall survival is defined as the time from the first dose of study treatment to death due to any cause. Participants who do not die will be censored on the date of the last study assessment or contact.

Pharmacokinetic endpoints include serum concentrations of MK-5890 and pembrolizumab and derived PK parameters.

10.4.2 Safety Endpoints

The primary safety endpoint is the number/proportion of participants with DLT(s), AE(s), and who discontinue study treatment due to AE(s). In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including laboratory tests and vital signs.

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

10.5 Analysis Populations

10.5.1 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 will include ASaT participants who meet the criteria for DLT evaluability (eg, finished DLT evaluation period without a DLT or experienced a DLT in DLT evaluation period). See Section 7.2.2 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.

Safety data from participants who experience disease progression in the monotherapy arms and cross-over into the MK-5890 + pembrolizumab combination arm will be presented separately.

10.5.2 Pharmacokinetic Analysis Populations

The Per-Protocol (PP) population will be used for the analysis of PK and target engagement 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 in the CSR, along with the reasons for exclusion. At the end of the study, all participants who were compliant with the study procedures and have available data from at least 1 dose of study treatment may be included in the PP analysis dataset.

10.5.3 Efficacy Analysis Populations

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

Efficacy data from participants who experience disease progression in the monotherapy arms and cross-over into the MK-5890 + pembrolizumab combination arm will be presented separately.

10.6 Statistical Methods

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

10.6.1 Statistical Methods for Efficacy Analysis

For the secondary endpoint of ORR as assessed by the investigator based on RECIST 1.1, the point estimate and 95% confidence interval will be evaluated separately in participants treated with MK-5890 monotherapy (Arm 1a), participants treated with MK-5890 in combination with pembrolizumab (Arms 2a, 2b, and 2c), and participants treated with MK-5890 in combination with pembrolizumab and nab-paclitaxel (Arm 4) using exact binomial distribution. Pairwise comparison will be conducted for ORR among participants with endometrial cancer treated in Arm 1a (30 mg MK-5890 Q3W), Arm 2b (30 mg MK-5890 in combination with 200 mg pembrolizumab Q3W), and Arm 2c (30 mg MK-5890 in combination with 400 mg pembrolizumab Q6W) using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The statistical methods for the tertiary/exploratory efficacy endpoints will be documented in a separate 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.

Adverse events will be summarized by counts and frequencies for each treatment arm and dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate (eg, counts, percentages).

In the dose escalation and confirmation phase (Arm 1, Arm 2 and Arm 3) and the dose expansion phase (Arm 4), DLTs will be listed and summarized by treatment arm and dose level. The pool-adjacent-violators algorithm [Ji, Y. and Wang, S.-J. 2013], which forces the DLT rate estimates to be non-decreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at each tested dose level of MK-5890 and the 80% Bayesian credible intervals based on a prior distribution of Beta (1,1) for the estimates will be provided.

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

10.6.3.1 Demographic and Baseline Characteristics

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

10.6.3.2 CCI

CCI

10.7 Interim Analyses

In the dose escalation and confirmation phase (Arm 1, Arm 2 and Arm 3) and the dose expansion phase (Arm 4), data will be examined on a continuous basis to allow for dose-finding decisions using the mTPI design.

In the dose expansion phase, the totality of the data will be examined once the first 15 participants with TNBC in Arm 2a are enrolled and have at least 1 post-baseline scan to decide whether or not to continue enrollment to 30 participants. CCI

In addition, the totality of the data will be examined once the first 10 participants with endometrial cancer per treatment arm are enrolled and have at least 1 post-baseline scan to decide whether or not to continue enrollment to 20 participants in that arm. CCI

The totality of the data will be examined once the first 20 participants with TNBC in Arm 4 are enrolled and have at least 1 post-baseline scan to decide whether or not to continue enrollment to 40 participants in Arm 4 CCI

CCI

[redacted]

Other interim analyses (eg, for efficacy) may be conducted to enable future study planning at the Sponsor's discretion.

10.8 Multiplicity

There will be no multiplicity control in this study.

10.9 Sample Size and Power Calculations

During the dose escalation and confirmation phase, approximately 72 participants are expected to be enrolled (62 participants in Arms 1 and 2, and 10 participants in Arm 3). The actual sample size will depend on the safety profile of MK-5890 in each treatment arm but is expected to be in line with a typical Phase 1 first-in-human oncology study. In the dose expansion phase, approximately 130 participants are expected to be enrolled, including 30 participants with TNBC in Arm 2a, 60 participants with endometrial cancer (20 participants per arm) and 40 participants with TNBC in Arm 4. The actual sample size will depend on the safety profile of MK-5890 in combination with pembrolizumab and nab-paclitaxel (Arm 4) and efficacy profile in each arm. In total, approximately 202 participants will be used for study planning purposes.

CCI

[redacted]

CCI [redacted]

10.10 Subgroup Analyses

Efficacy endpoints will be analyzed by arm, dose level, and tumor type. CCI [redacted]

10.11 Compliance (Medication Adherence)

Compliance data for study treatment will be collected during the study. 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

[Ahrends, T., et al 2016]	Ahrends T, Babala N, Xiao Y, Yagita H, van Eenennaam H, Borst J. CD27 Agonism Plus PD-1 Blockade Recapitulates CD4+ T-cell Help in Therapeutic Anticancer Vaccination. Cancer Res. 2016 May 15;76(10):2921-31.	[04QSJQ]
[Borst, J., et al 2005]	Borst J, Hendriks J, Xiao Y. CD27 and CD70 in T cell and B cell activation. Curr Opin Immunol. 2005 Jun;17(3):275-81.	[04QRF9]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Coquet, J. M., et al 2013]	Coquet JM, Ribot JC, Bąbała N, Middendorp S, van der Horst G, Xiao Y, et al. Epithelial and dendritic cells in the thymic medulla promote CD4+Foxp3+ regulatory T cell development via the CD27-CD70 pathway. J Exp Med. 2013 Apr 8;210(4):715-28.	[04QRGJ]
[Emens, L. A. and Middleton, G. 2015]	Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res. 2015 May;3(5):436-43.	[04BLP8]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Galluzzi, L., et al 2015]	Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted Anticancer agents. Cancer Cell. 2015 Dec 14;28(6):690-714.	[04NCRQ]
[Gandhi, L., et al 2018]	Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018 May 31;378(22):2078-92.	[04ZK0V]

[Gradishar, W. J., et al 2005]	Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005 Nov 1;23(31):7794-803.	[04BLPK]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Hishima, T., et al 2000]	Hishima T, Fukayama M, Hayashi Y, Fujii T, Ooba T, Funata N, et al. CD70 expression in thymic carcinoma. Am J Surg Pathol. 2000 May;24(5):742-6.	[04QRLX]
[Ji, Y. and Wang, S.-J. 2013]	Ji Y, Wang S-J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol 2013;31:1-12.	[03FL3C]
[Ji, Y., et al 2007]	Ji Y, Li Y, Bekele BN. Dose-finding in phase l clinical trials based on toxicity probability intervals. Clin Trials 2007;4:235-44.	[03TFYL]
[Kang, C. and Syed, Y. Y. 2020]	Kang C, Syed YY. Atezolizumab (in combination with nab-paclitaxel): a review in advanced triple-negative breast cancer. Drugs. 2020;80:601-7.	[05NX2C]
[Kashii, Y., et al 1999]	Kashii Y, Giorda R, Herberman RB, Whiteside TL, Vujanovic NL. Constitutive expression and role of the TNF family ligands in apoptotic killing of tumor cells by human NK cells. J Immunol. 1999 Nov 15;163(10):5358-66.	[04QR0V]
[Langer, C. J., et al 2016]	Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Nov;17:1497-508.	[04W3BR]

[Lens, S. M., et al 1998]	Lens SM, Tesselaar K, van Oers MH, van Lier RA. Control of lymphocyte function through CD27-CD70 interactions. Semin Immunol. 1998 Dec;10(6):491-9.	[04QR0R]
[Ling, J., et al 2009]	Ling J, Zhou H, Jiao Q, Davis HM. Interspecies scaling of therapeutic monoclonal antibodies: initial look. J Clin Pharmacol 2009;49:1382-402.	[03RQ8X]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[00VMQY]
[Nolte, M. A., et al 2009]	Nolte MA, van Olffen RW, van Gisbergen KP, van Lier RA. Timing and tuning of CD27-CD70 interactions: the impact of signal strength in setting the balance between adaptive responses and immunopathology. Immunol Rev. 2009 May;229(1):216-31.	[04QRG7]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Orengo, A. M., et al 1997]	Orengo AM, Cantoni C, Neglia F, Biassoni R, Ferrini S. Reciprocal expression of CD70 and of its receptor, CD27, in human long term-activated T and natural killer (NK) cells: inverse regulation by cytokines and role in induction of cytotoxicity. Clin Exp Immunol. 1997 Mar;107(3):608-13.	[04QR0C]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]

[Rugo, H. S., et al 2020]	Rugo HS, Schmid P, Cescon DW, Nowecki Z, Im SA, Yusof MM, et al. Additional efficacy endpoints from the phase 3 KEYNOTE-355 study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy as first-line therapy for locally recurrent inoperable or metastatic triple-negative breast cancer [abstract]. Presented at: Virtual 2020 San Antonio Breast Cancer Symposium (SABCS); 2020 Dec 8-11; [online meeting]. Abstract no. GS3-01.	[05NTNW]
[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):e143-52.	[04P9RV]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Smith, T. J., et al 2006]	Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 2006;24(19):3187-205.	[00TGJC]
[U.S. Prescribing Information 2020]	U.S. Prescribing Information: KEYTRUDA (pembrolizumab) injection, for intravenous use: Nov 2020.	[05NX2D]
[van de Ven, K. 2015]	van de Ven K, Borst J. Targeting the T-cell co-stimulatory CD27/CD70 pathway in cancer immunotherapy: rationale and potential. Immunotherapy. 2015;7(6):655-67.	[04QRJB]
[Vincent, J., et al 2010]	Vincent J, Mignot G, Chalmin F, Ladoire S, Bruchard M, Chevriaux A, et al. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Res. 2010 Apr 15;70(8):3052-61.	[04NCS5]

[Zhang, X., et al 2004] Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47. [00VMQJ]

12. APPENDICES

12.1 Appendix 1: Study Governance Considerations

Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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 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 CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

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). In the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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 timeframe 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 a contraceptive method with a failure rate of <1% per year as described in Table 15 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
    - The following are not acceptable methods of contraception:
        - Periodic abstinence (calendar, symptothermal, 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 condom cannot be used together.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 15 during the protocol-defined timeframe in Section 6.1.

Table 15 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) 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 MK-5890 or pembrolizumab OR 180 days after the last dose of chemotherapeutic agents. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those that inhibit ovulation.

Pregnancy Testing

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

Following initiation of study treatment additional pregnancy testing will be performed at monthly intervals during the treatment period and 120 days after the last dose of MK-5890 or pembrolizumab OR 180 days after the last dose of chemotherapeutic agents as required by local regulations.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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 <u>Meeting</u> 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). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

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 4.0 or later. 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 16 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 6.1 and Section 6.2 of the protocol, respectively.
- Investigators must document their review of each laboratory safety report.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 16 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)
	Lactate Dehydrogenase (LDH)	Amylase	Lipase	
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]			

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.

12.6 Appendix 6: Country-Specific Requirements

Not applicable.

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 disease progression by RECIST 1.1 as determined by the investigator, the investigator will decide whether or not to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 12 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 progressive disease, and is not required to have repeat tumor imaging for confirmation of disease progression 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 disease progression by iRECIST, per investigator assessment.

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

- Increase in the sum of diameters of target lesion(s) identified at baseline of ≥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; or
- Development of new lesion(s).

iRECIST defines new response categories, including unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD). 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 Scan

On the confirmatory imaging scan, 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 of ≥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 progressive disease by RECIST 1.1

Persistent iUPD

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

- None of the progression-confirming factors identified above occurs; AND
- The target lesion sum of diameters (initial target lesions) remains above the initial progressive disease 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 scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, or iSD/iPR/iCR.

Resolution of iUPD

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

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

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

In this case, the initial iUPD is considered to be 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 Scan

If repeat imaging does not confirm disease progression 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 disease progression is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals outlined in Section 2.

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 progressive disease 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 study, 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 Scan' above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial progressive disease, with 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].

12.8 Appendix 8: Abbreviations and Trademarks

Abbreviation/Term	Definition
1L	First-line
2L	Second-line
2L+	Two or more lines
ADA	Anti-drug antibody
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASaT	All-Subjects-as-Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BCG	Bacillus Calmette–Guérin
β-hCG	β-human chorionic gonadotropin
CAP	College of American Pathologists
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CPS	Combined Positive Score
CR	Complete response
CRF	Case report form
CSF	Colony-stimulating factor
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
D	De-escalate to the next lower dose
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DU	Unacceptably toxic dose
ECG	Electrocardiogram
ECI	Event(s) of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ELISA	Enzyme-linked immunoassay
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set

Abbreviation/Term	Definition
FBR	Future biomedical research
FDAA	Food and Drug Administration Amendments Act
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HER-2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST confirmed progressive disease
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IM	Intramuscular
INR	International normalized ratio
IO	Immuno-oncology
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified RECIST 1.1 for immune-based therapeutics
iSD	iRECIST stable disease
ITT	Intent To Treat
iUPD	iRECIST unconfirmed progressive disease
IV	Intravenous
IVD	In vitro diagnostic
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
mBC	metastatic breast cancer
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSI	Microsatellite instability
MTD	Maximum tolerated dose
mTPI	modified toxicity probability interval
Nab-paclitaxel	Nanoparticle albumin-bound paclitaxel

Abbreviation/Term	Definition
NCI	National Cancer Institute
NK	Natural killer
NOAEL	No observed adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic(s)
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PP	Per-Protocol
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Every 3 weeks
Q6W	Every 6 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SNP	Single nucleotide polymorphism
SoA	Schedule of Activities
sSAP	Supplementary Statistical Analysis Plan
TCR	T cell receptor
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
TPI	Toxicity probability interval
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US FDA	United States Food and Drug Administration
WOCBP	Woman of childbearing potential

12.9 MASCC 2016 Guidelines

DEXAMETHASONE		Dose and Schedule
High Risk	- Acute Emesis	20 mg once (12 mg when used with (fos)aprepitant or netupitant)**
	- Delayed Emesis	8 mg bid for 3 - 4 days (8 mg once daily when used with (fos)aprepitant or netupitant)
Moderate Risk	- Acute Emesis	8 mg once
	- Delayed Emesis	8 mg daily for 2 - 3 days (many panelists give the dose as 4 mg bid)
Low Risk	- Acute Emesis	4 - 8 mg once

* While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.

** The 12 mg dose of dexamethasone is the only one tested with (fos)aprepitant/netupitant in large randomized trials.

Rolia F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol (2016) 27 (suppl_5): v119-v133, 2016.

http://www.mascc.org/antiemetic-guidelines

Investigators may use local equivalent or more current guidelines, if available.