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* Includes the 159 sites at which at least one participant was randomly allocated to study treatment and the 9 sites that screened at least one participant but did not have any randomly allocated to study treatment.

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Title Page

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Protocol Title: A Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE 811)

Protocol Number: 811-06

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

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

One Merck Drive
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Regulatory Agency Identifying Number(s):

IND NUMBER: 123,482

EudraCT NUMBER: 2018-000224-34

Approval Date: 07 July 2020

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	07-JUL-2020	Update SAP language to remove PFS analysis for IA1 in response to Regulatory Authority Input.
Amendment 5	20-MAY-2020	Update protocol and SAP language regarding the definition of the curative surgical resection and modification of PFS primary censoring rule associated with the curative surgical resection, remove the ORR futility analysis for IA1, and add a PFS analysis for IA1.
Amendment 4	27-FEB-2019	Update Biomarker Collection Information.
Amendment 3	24-JAN-2019	Response to Regulatory Authority Input.
Amendment 2	16-AUG-2018	Response to Regulatory Authority Input.
Amendment 1	31-MAY-2018	Response to Regulatory Authority Input.
Original Protocol	11-APR-2018	N/A.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 06

Overall Rationale for the Amendment:

Update SAP language to remove PFS analysis for IA1 in response to Regulatory Authority Input.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Changed "will" to "may" in regard to participants entering an extension study.	Rollover into extension study is not mandatory.
1.3.1 Initial Treatment Phase	Revised note for thyroid tests to "Should be performed at Screening and within 72 hours prior to dosing on Day 1 of every other Cycle starting from Cycle 2."	Clarification that thyroid testing samples can be drawn within 72 hours prior to dosing on every other cycle after C1D1.

Section # and Name	Description of Change	Brief Rationale
1.3.2 Second Course Phase (Retreatment with Pembrolizumab)	Revised note for thyroid tests to "Should be performed at C1D1 and within 72 hours prior to dosing on Day 1 of every other Cycle starting from Cycle 2."	Clarification that thyroid testing samples can be drawn within 72 hours prior to dosing on every other cycle after C1D1.
4.2.1.1.2 Secondary Efficacy Endpoints	Updated section number.	Correction of mislabeled section number.
6.5.3 Curative Surgery	Updated reference from Section 7.1 to Section 8.2.1.2 and Section 8.2.1.3.	Correction of section number reference.
9.1 Statistical Analysis Plan Summary 9.7.1 Efficacy Interim Analysis	Removed PFS endpoint from the 1st interim analysis as an administrative look.	Based on Regulatory Authority input, the data will be immature for PFS at IA1 when the enrollment is not completed.

Section # and Name	Description of Change	Brief Rationale
9.8.2 Progression-free Survival	Updated Table 23 after removal of PFS endpoint from the 1st interim analysis.	Based on Regulatory Authority input, efficacy boundaries and properties of PFS endpoint needs to be updated after removal of PFS endpoint from IA1.

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[redacted]

1. Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE 811)

Short Title:
Pembrolizumab/Placebo Plus Trastuzumab Plus Chemotherapy in HER2 Positive Advanced Gastric or GEJ Adenocarcinoma

Objectives/Hypotheses and Endpoints:

In male and female participants at least 18 years of age with previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To compare PFS between treatment groups. • Hypothesis (H1): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone in terms of PFS per RECIST 1.1 as assessed by blinded independent central review (BICR).	• PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
• Objective: To compare overall survival (OS) between treatment groups. • Hypothesis (H2): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy in terms of OS.	• OS: The time from randomization to death due to any cause.

This study will be considered to have met its success criteria if the experimental arm is superior to the control arm with respect to PFS or OS.	
Secondary Objectives	
• Objective: To compare Objective Response Rate (ORR) between treatment groups. • Hypothesis (H3): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy in terms of ORR per RECIST 1.1 as assessed by BICR.	• Objective Response: Complete response (CR) or partial response (PR)
• Objective: To estimate Duration of Response (DOR), per RECIST 1.1 as assessed by BICR for each treatment group.	• DOR: For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
• Objective: To assess the safety and tolerability of pembrolizumab in combination with trastuzumab plus chemotherapy by proportion of adverse events (AEs)	• Adverse events • Discontinuation of study treatment due to AEs

Overall Design:

Study Phase	Phase 3
Clinical Indication	Advanced Gastric or GEJ Adenocarcinoma
Population	Human epidermal growth factor receptor 2 (HER2) positive participants with advanced gastric or GEJ adenocarcinoma
Study Type	Interventional
Type of Design	Randomized, Multi-site, Parallel-group
Type of Control	Placebo and active control
Study Blinding	Double-blind
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant signs the informed consent until the last participant's last study-related contact or visit.

Number of Participants:

Approximately 692 participants will be randomized in the Global Cohort. A separate cohort of approximately 40 participants will enroll in the Japan-specific SOX (S-1 combination product plus oxaliplatin) cohort.

Treatment Groups and Duration:

Treatment Groups	Trastuzumab and pembrolizumab plus either cisplatin plus 5-FU (FP) or oxaliplatin plus capecitabine (CAPOX) Trastuzumab and placebo plus FP and CAPOX Japan-specific SOX Cohort: Trastuzumab and pembrolizumab plus SOX Trastuzumab and placebo plus SOX

Duration of Participation	Each participant will participate in the trial from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive trial treatment until disease progression is radiographically documented and verified by BICR, when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with trial treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab/placebo. Participants who stop trial treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a CR and stop trial treatment, may be eligible for up to 17 additional administrations of pembrolizumab upon experiencing disease progression if they are randomized to the pembrolizumab arm. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 and verified by BICR and confirmed by the site per iRECIST (for participants treated with pembrolizumab), initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. Once the participant has achieved the study objective or study has ended, the participant is discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

Study Governance:

Study Governance Committees	

Committee	**Included in this study?**
Steering Committee	N
Executive Oversight Committee	Y
Data Monitoring Committee	Y
Clinical Adjudication Committee	N

Study governance considerations are outlined in Appendix 1.

A list of abbreviations used in this document can be found in Appendix 7.

1.2 Schema

The Global Cohort study design is depicted in Figure 1, and the Japan-specific SOX cohort study design is depicted in Figure 2.

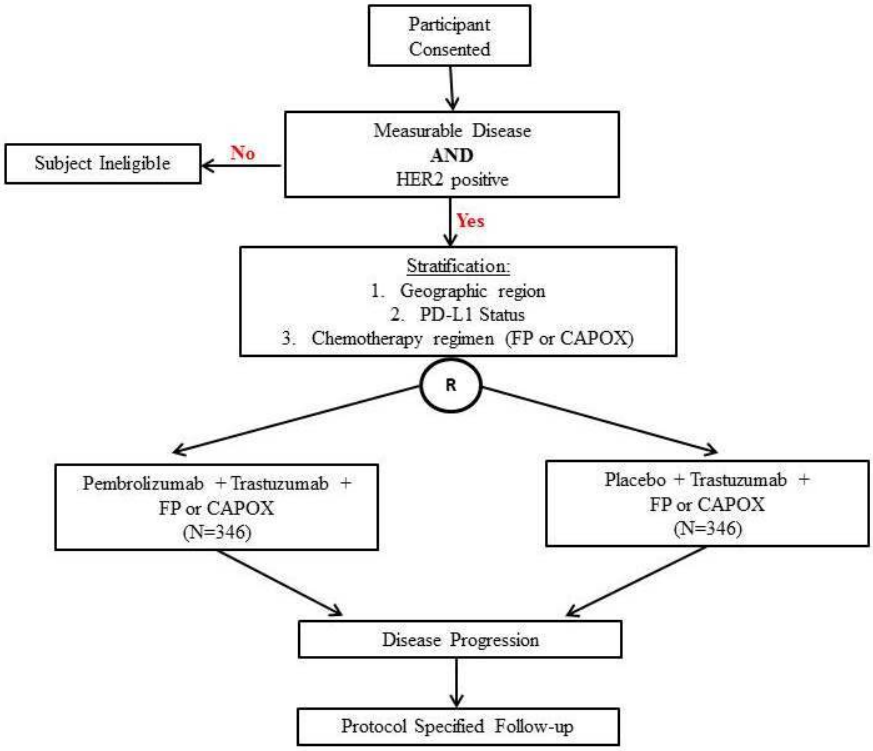


Figure 1 Global Trial Design

Figure 1 includes Japan participants using the FP or CAPOX chemotherapy regimens.

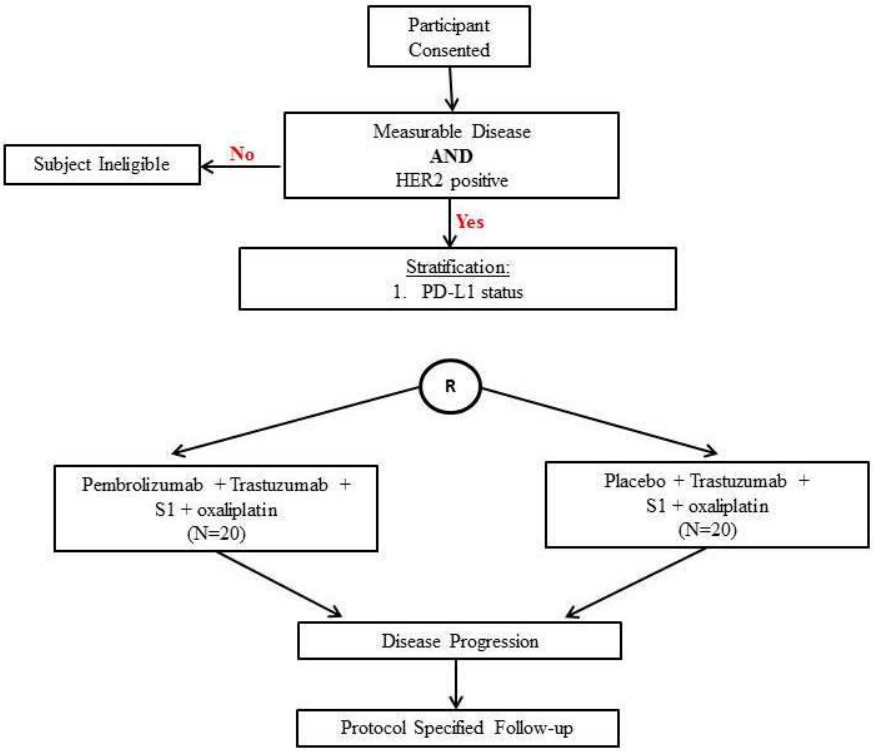


Figure 2 Japan-specific SOX Cohort Trial Design

Figure 2 includes Japan participants using the SOX chemotherapy regimen. This cohort is only open in Japan.

1.3 Schedule of Activities (SoA)

1.3.1 Initial Treatment Phase

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Administrative Procedures													
Informed Consent	X[a]												
Re-consent at the first indication of radiographic progression													As assessed by the investigator
Informed Consent for Future Biomedical Research	X												Not required for participation in trial
Participant Identification Card	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Prior and Concomitant Medication Review	X		X	X	X	X	X	X	X	X			Concomitant medications will be recorded beyond 30 days post-treatment discontinuation if related to an SAE or ECI.
Treatment Assignment in IRT			X										The treatment eligibility assessment must be completed prior to randomization. The investigator must decide the choice of intervention and provide the rationale prior to randomization.
Tumor Tissue Collection													
Archival or Newly Obtained Tissue Collection	X												

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
On-treatment Biopsy (Optional)				X									Additional optional biopsy tissue may be collected around 3-6 weeks after first dose of treatment if allowed by local regulations
Trial Treatment Administration													
Pembrolizumab/Placebo			X	X	X	X	X	X					
FP or CAPOX (Global)			X	X	X	X	X	X					
SOX (Japan Only)			X	X	X	X	X	X					
Trastuzumab			X	X	X	X	X	X					

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Efficacy Procedures													
Tumor Imaging	X				X		X	X	X		X		The initial imaging must be done within 28 days of randomization. The first on-study imaging assessment should be performed 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 1 year, participants who remain on treatment will have imaging performed every 6 weeks.

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Safety Procedures													
Full Physical Examination	X								X				
Directed Physical Examination			X	X	X	X	X	X					
Vital Signs (pulse, blood pressure, respiratory rate and temperature), Height and Weight	X		X	X	X	X	X	X	X				Height is measured at the Initial Screening Visit only.
Audiometry	X												For participants receiving FP only. Repeated during the trial as clinically indicated
12-lead ECG	X												6-lead ECG is allowed per institutional standard.

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
ECHO or MUGA (LVEF)	X				X		X	X					Initial LVEF must be performed within 14 days prior to C1D1. Repeat LVEF assessments will be performed at Cycles 3 and 5 and every 4 cycles starting from Cycle 9.
TB, HIV, and hepatitis B and C determination	X												No testing for TB, HIV, Hep B, and Hep C is required unless mandated by local health authority. TB, HIV, Hep B, and Hep C testing is mandatory in Germany and the UK (Appendix 6).

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
ECOG Performance Status		X		X	X	X	X	X	X		X		ECOG Status must be performed **within 3 days** of beginning of Cycle 1 and prior to each treatment administration.
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X		
Post-study Anticancer Therapy Status											X	X	
Survival Status		<----------									---------->	X	

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Laboratory Procedures/Assessments													
Pregnancy Test – Urine or Serum		X		X	X	X	X	X	X	X			For women of reproductive potential, a urine pregnancy test should be performed at screening, within 72 hours prior to each cycle of trial treatment, and 30 days post treatment. A serum test can be considered if urine is not conclusive. Pregnancy tests (serum and/or urine tests) should also be repeated as required by local guidelines.
PT/INR and aPTT		X											PT/INR should be tested as needed for participants on warfarin-based anti-coagulation therapy.

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
CBC with Differential		X		X	X	X	X	X	X	X			Screening CBC and chemistry tests must be performed within 10 days of C1D1 and within 72 hours prior to dosing in other cycles.
Comprehensive Chemistry Panel		X		X	X	X	X	X	X	X			
T3, FT4, and TSH	X			X		X		X		X			Should be performed at Screening and within 72 hours prior to dosing on Day 1 of every other Cycle starting from Cycle 2. Participants may be dosed in subsequent cycles after C1D1 while thyroid function tests are pending.
Urinalysis	X												

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Pharmacokinetics/Pharmacodynamics/ Biomarkers													
Blood for RNA Analysis			X	X			X		X				Collect predose
Whole Blood Sample for MSI DNA Analysis[b]			X										Use an EDTA tube. If sample is not available at C1D1 it must be collected at a subsequent visit.
Blood for Genetic Analyses			X										See Section 8.7
Blood for Plasma Biomarker Analyses			X	X			X		X				Collect predose
Blood for Serum Biomarker Analyses			X	X			X		X				Collect predose
Blood for ctDNA			X	X			X		X				Collect predose
Blood for Serum pembrolizumab PK			X	X		X		X					c
Blood for ADA of pembrolizumab			X	X		X		X					c

Trial Period	**Screening Phase**		**Treatment Cycles**						**End of Treatment**	**Post-treatment**			**Notes**
Treatment Cycle/Title			**1**	**2**	**3**	**4**	**5**	**6 & Beyond**	**Discontin-uation**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**	
Scheduled Day, Week	**-28 to -1**	**-10 to -1**	**1**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**1 ±3**	**At time of Discontin-uation**	**30 days post- Last Dose +7**	**Every 6 weeks ±7 days**	**Every 12 weeks ±14 days**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Blood for Serum trastuzumab PK			X	X		X		X					d
Blood for ADA of trastuzumab			X	X		X		X					d
Patient-reported Outcomes													
EuroQoL EQ-5D/ EORTC QLQ-C30, EORTC QLQ-STO22			X	X	X	X	X	Odd cycles	X	X			e

ADA = Anti-drug Antibodies; aPTT = activated partial thromboplastin time; C1 = Cycle 1, etc.; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; DC = discontinuation; DMFS = distant metastasis-free survival; ECG = electrocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; IRT = Interactive Response Technology; LDH = Lactic Acid Dehydrogenase; MRI = magnetic resonance imaging; PET-CT = positron emission tomography -computed tomography; PK = Pharmacokinetic; PRO = patient-reported outcome; PT/INR = prothrombin time/international normalized ratio; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid stimulating hormone; TX = Treatment.

a. Written consent must be obtained prior to performing any protocol-specified procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg, within 28 days prior to the first dose of trial treatment). Authorization for release of tumor tissue form may be signed prior to the Screening Period specified above (-28 to -1 days) to allow the submission of archival tissue sample for determination of HER2 and PD-L1 status and is expected to comply with all IRB/IEC requirements.

b. In order to perform MSI analysis by PCR, normal and tumor tissue is required. A blood sample (normal/non-tumor tissue) is collected to extract normal DNA for comparison testing to tumor DNA in MSI analysis. Both tumor tissue and blood sample are required to perform central MSI testing by PCR.

c. PK/ADA of pembrolizumab: Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, and 8, every 4 cycles thereafter, and until discontinuation of study treatment (or until the participant starts new anti-cancer therapy). Samples should be drawn within 24 hours prior to infusion of pembrolizumab. Additional post-dose (peak) PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8.

d. PK/ADA of trastuzumab: Pre-dose trough PK and anti-trastuzumab antibody samples will be collected at Cycles 1, 2, 4, and 8, every 4 cycles thereafter, and until discontinuation of study treatment (or until the participant starts new anti-cancer therapy). Samples should be drawn within 24 hours prior to infusion of trastuzumab. Additional post-dose (peak) PK samples will be drawn within 30 minutes after end of trastuzumab infusion at Cycles 1 and 8. PK/ADA samples of trastuzumab will be collected for both arms.

e. It is strongly recommended that electronic patient-reported outcomes (ePROs) are administered prior to drug administration, AE evaluation, and disease status notification, starting with the EQ5D-5L, followed by EORTC QLQ-C30, and EORTC QLQ-STO22; an exception to this recommendation may occur at the treatment discontinuation visit where participants may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All ePROs are to be performed at Cycles 1, 2, 3, 4, and 5 and every 2 cycles thereafter (eg, Cycle 7, Cycle 9) up to a year or End of Treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit. If the participant does not complete the ePROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed. A visit window of ± 7 days will apply to PRO visit assessment.

1.3.2 Second Course Phase (Retreatment with Pembrolizumab)

Trial Period:	**Treatment Cycles**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle:	**1**	**2**	**3**	**4**	**5**	**Cycle 6 and beyond**	**Last Dose**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-up**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
							At time of treatment discontinuation	**30 days post last dose**	**Every 6 weeks post discontinuation**	**Every 12 weeks**	
Scheduling Window (Days):		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 7**	**± 7**	**± 14**	
Administrative Procedures											
Eligibility Criteria	X										
Concomitant Medication Review	X	X	X	X	X	X	X	X			
Clinical Procedures/Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X						X				
Directed Physical Examination		X	X	X	X	X					
Vital Signs (pulse, blood pressure, respiratory rate, and temperature) and Weight	X	X	X	X	X	X	X				

Trial Period:	**Treatment Cycles**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle:	**1**	**2**	**3**	**4**	**5**	**Cycle 6 and beyond**	**Last Dose**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-up**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
							At time of treatment discontinuation	**30 days post last dose**	**Every 6 weeks post discontinuation**	**Every 12 weeks**	
Scheduling Window (Days):		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 7**	**± 7**	**± 14**	
ECOG Performance Status	X	X	X	X	X	X	X				ECOG Status must be performed **within 3 days** of beginning of Cycle 1 and prior to each treatment administration.
Pembrolizumab Administration	X	X	X	X	X	X					In addition to pembrolizumab, the participant may also resume the previously administered chemotherapy backbone and/or trastuzumab at the discretion of the site investigator.
Post-study Anticancer Therapy Status									X	X	
Survival Status	<----------								---------->	X	

Trial Period:	**Treatment Cycles**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle:	**1**	**2**	**3**	**4**	**5**	**Cycle 6 and beyond**	**Last Dose**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-up**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
							At time of treatment discontinuation	**30 days post last dose**	**Every 6 weeks post discontinuation**	**Every 12 weeks**	
Scheduling Window (Days):		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 7**	**± 7**	**± 14**	
Laboratory Procedures/Assessments: Analyses performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum	X	X	X	X	X	X	X	X			A
PT/INR and aPTT	X										PT/INR should be tested as needed for participants on warfarin-based anti-coagulation therapy.
CBC with Differential	X	X	X	X	X	X	X	X			B
Chemistry Panel	X	X	X	X	X	X	X	X			B
Urinalysis	X										B

Trial Period:	**Treatment Cycles**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle:	**1**	**2**	**3**	**4**	**5**	**Cycle 6 and beyond**	**Last Dose**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-up**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
							At time of treatment discontinuation	**30 days post last dose**	**Every 6 weeks post discontinuation**	**Every 12 weeks**	
Scheduling Window (Days):		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 7**	**± 7**	**± 14**	
T3 (or Free T3), FT4, and TSH	X	X		X		X		X			Should be performed at C1D1 and within 72 hours prior to dosing on Day 1 of every other Cycle starting from Cycle 2. Participants may be dosed in subsequent cycles after C1D1 while thyroid function tests are pending.
Efficacy Measurements											
Tumor Imaging	X		X		X	X	X		X		

ADA = Anti-drug Antibodies; aPTT = activated partial thromboplastin time; C1 = Cycle 1, etc.; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; DC = discontinuation; DMFS = distant metastasis-free survival; ECG = electrocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; IRT = Interactive Response Technology; LDH = Lactic Acid Dehydrogenase; MRI = magnetic resonance imaging; PET-CT = positron emission tomography -computed tomography; PK = Pharmacokinetic; PRO = patient-reported outcome; PT/INR = prothrombin time/international normalized ratio; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid stimulating hormone; TX = Treatment.

a. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to each cycle of trial treatment, and 30 days post treatment. A serum test can be considered if urine is not conclusive. Pregnancy tests (serum and/or urine tests) should also be repeated as required by local guidelines.

b. CBC, UA, and Chemistry tests must be performed within 7 days of C1D1. CBC, UA, and Chemistry tests do not need to be repeated on C1D1 if they have been conducted within 72 hours prior to dosing at screening. Lab samples can be collected up to 72 hours prior to the scheduled time point. CBC and Chemistry tests should be performed every other cycle starting from Cycle 8.

2. Introduction

Gastric cancer remains a major health problem worldwide. Gastric cancer is the fifth most common cancer in the world and is a major cause of cancer-related death [Ferlay, J., et al 2014]. There were approximately one million new cases of gastric cancer worldwide in 2012 (631,000 men, 320,000 women), with 723,000 deaths (469,000 men, 254,000 women), making it the third-leading cause of cancer death globally in both sexes [Ferlay, J., et al 2014]. Age-standardized incidence rates are about twice as high in men as in women. Gastric cancer incidence varies markedly by geographic region. More than 70% of cases occur in developing countries, and half the world total occurs in Eastern Asia. In the European Union, incidence and mortality for gastric cancer were estimated at 82,000 (51,000 in males and 31,000 in females) and 58,000 (35, 000 in males and 23,000 in females), respectively in 2012 [Ferlay, J., et al 2014]. In the United States (US), incidence and mortality estimated at 21,000 (13,000 in males and 8,000 in females) and 12,000 (7,000 in males and 5,000 in females), respectively in 2012 [Ferlay, J., et al 2014].

Human epidermal growth factor receptor 2 (HER2, ErbB2) is a transmembrane tyrosine kinase receptor and is overexpressed or amplified in 10-20% of gastric cancer. Innate and adaptive immune mechanisms are emerging as key players in modulation of the effects of HER2-targeted agents such as trastuzumab. A growing body of preclinical and clinical evidence shows that the immune system contributes substantially to the therapeutic effects of trastuzumab in solid tumors [Bellati, F., et al 2010] [Ferris, R. L., et al 2010]. In addition, there is strong rationale in exploring the impact of combining trastuzumab with an anti-PD-1 inhibitor like pembrolizumab in HER2 positive cancer.

2.1 Study Rationale

Systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer (see NCCN [National Comprehensive Cancer Network 2013] and ESMO [Cunningham, D. 2008] treatment guidelines). Platinum/fluoropyrimidine doublet regimens containing cisplatin or oxaliplatin and 5-FU or capecitabine are the most commonly used regimens worldwide as standard first-line (1L) chemotherapy regimens for patients with metastatic disease. Trials have demonstrated similar efficacy among these doublet chemotherapy regimens in advanced gastric cancer. Patients with HER2 positive tumors receive a greater benefit when treated with trastuzumab-containing regimens [Kanagavel, D., et al 2015]. Estimates of HER2 positive prevalence in gastric cancer range from 6% to 34% [Ghosn, M., et al 2016] [Kelly, C. M. 2016].

The Trastuzumab for Gastric Cancer (ToGA) trial was the first randomized, prospective, multicenter, Phase 3 trial to evaluate the efficacy and safety of trastuzumab in HER2 positive gastric/GEJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine [Bang, Y. J., et al 2010]. In this study, 594 patients were randomly assigned to study treatment (trastuzumab plus chemotherapy, n=298; chemotherapy alone, n=296). Overall survival (OS), the primary endpoint, was statistically significant in the trastuzumab plus chemotherapy arm compared with the chemotherapy alone arm ($p = 0.0045$, log-rank test; hazard ratio [HR], 0.74). The median survival time was 13.8 months in the trastuzumab plus

chemotherapy arm and 11.1 months in the chemotherapy alone arm and the risk of death was decreased by 26% for patients in the trastuzumab plus chemotherapy arm.

Based on the ToGA trial, the current standard of care is to use trastuzumab in HER2+ advanced gastric cancer patients in combination with fluoropyrimidine (5-FU or capecitabine) and platinum (cisplatin or oxaliplatin) containing doublet regimen. Given similar efficacy expected from these regimens, the choice between these regimens is made based on patients' general medical condition and comorbidities in consideration of different toxicity profiles of the regimens. This practice pattern is supported by global consensus guidelines in treatment of advanced gastric cancer which recommend use of any of the doublets of choice discussed above, plus trastuzumab in patients with HER2 positive gastric cancers [National Comprehensive Cancer Network 2016] [Cunningham, D. 2008].

Since the results of ToGA were reported, no further advance has been made in treatment of HER2 positive 1L gastric cancer patients. Duration of clinical benefit with current standard of care is limited as evidenced by duration of response (DOR) and mean progression-free survival (PFS) shorter than 7 months [Bang, Y. J., et al 2010] [Tabernero, J., et al 2017]. The majority of these patients develop intrinsic or acquired resistance within 1 year. Therefore, novel therapeutic approaches to overcome drug resistance are warranted to improve the survival outcome of these patients with HER2 positive tumors.

Clinical activity of pembrolizumab in advanced gastric cancer

Immune checkpoint inhibitors such as pembrolizumab have demonstrated durable immune-mediated anti-tumor activity in patients with advanced gastric cancer. Clinical proof of concept for pembrolizumab in these patients was demonstrated in Cohort D of the Phase 1b trial, KEYNOTE-012, which enrolled 39 patients with gastric or GEJ tumors expressing PD-L1 assessed using a prototype PD-L1 immunohistochemistry assay [Muro, K., et al 2016]. Eight of 39 patients had an objective response by RECIST 1.1 using central radiologic review for an objective response rate (ORR) of 22% (95% CI: 10, 39). Cohort 1 of the Phase II study, KEYNOTE-059 tested pembrolizumab monotherapy in a larger cohort of patients whose tumors had progressed on 2 or more lines of systemic therapy (3L+ patients). In this study, pembrolizumab monotherapy demonstrated clinically meaningful ORR in this heavily treated population for whom there are no other effective agents. Durable objective responses were observed in all comer population regardless of PD-L1 status with ORR of 12%, while a higher response rate (16%) was observed in the PD-L1 positive population [Wainberg, Z. A., et al 2017]. Based on data from KN059, pembrolizumab received accelerated approval by the US Food and Drug Administration (FDA) in September 2017 for treatment of 3L+ patients with tumors expressing PD-L1 (CPS $\geq$ 1) assessed by an FDA-approved test. KN059 included 2 additional cohorts where pembrolizumab was tested in 1L gastric cancer patients either as monotherapy (Cohort 3) or in combination with a fluoropyrimidine and cisplatin (Cohort 2). Cohort 3 enrolled 31 patients whose tumors expressed PD-L1 (CPS $\geq$ 1). Cohort 2 enrolled patients irrespective of PD-L1 expression (all-comers). In both cohorts, ORR was assessed according to RECIST 1.1 by independent central radiological review. The combination of pembrolizumab with cisplatin and 5-FU or

capecitabine in Cohort 2 (N=25) yielded an ORR of 60% (95% CI: 39, 79%) and a disease control rate (DCR) of 80% (95% CI: 59%, 93%). Responses were observed regardless of PD-L1 status. Median OS in Cohort 2 was 13.8 months (95% confidence interval [CI]: 8.6, NR). Monotherapy in PD-L1 positive 1L patients (Cohort 3) yielded an ORR of 26% (95% CI: 12, 45); median OS was 20.7 months (9.2, 20.7) [Loi, S., et al 2017].

KEYNOTE-061 (NCT02370498) was a global Phase 3 study of pembrolizumab versus paclitaxel for previously treated advanced gastric/GEJ cancer. Pembrolizumab reduced the risk of death by 18% vs paclitaxel in patients with PD-L1 CPS ≥1, although this difference was not statistically significant. Durable benefit of pembrolizumab was demonstrated in this trial. After median follow-up of 8 months, 7.8% of patients completed or remained on pembrolizumab, vs 0% on paclitaxel. Median OS was 9.1 months with pembrolizumab vs. 8.3 months with paclitaxel; the difference did not reach statistical significance (HR 0.82, one-sided p=.042). Twelve-month OS rates were 39.8% with pembrolizumab versus 27.1% with paclitaxel; 18-month OS rates were 25.7% versus 14.8%. There was no difference in PFS or ORR, but pembrolizumab responses were more durable: median duration of response was 18 months and 5.2 months for pembrolizumab and paclitaxel, respectively.

Taken together, the data show that pembrolizumab demonstrated durable clinical benefit and favorable tolerability in advanced gastric cancer populations. In the context of the proposed trial, it is important to note that pembrolizumab was safe in combination with chemotherapy and demonstrated high level of tumor responses regardless of PD-L1 status.

Mechanistic rationale for the use of pembrolizumab for the treatment of HERer2+ gastric cancer in combination with trastuzumab plus chemotherapy

A growing body of preclinical and clinical evidence shows that the immune system contributes substantially to the therapeutic effects of trastuzumab in solid tumors. HER2 positive cancers have high levels of T cell infiltration [Loi, S., et al 2013]. The immune system plays a key role in the mechanism of action of trastuzumab, an anti-HER2 mAb, through ADCC and recruitment of natural killer (NK) cells. Specifically, evidence indicates association between immune signature/extent of tumor-infiltrating lymphocytes and response to trastuzumab [Kohrt, H. E., et al 2012] [Kohrt, H. E., et al 2014].

Trastuzumab upregulates immune cell function, eg, NK cell degranulation and cytotoxicity, which in turn can enhance anti-tumor immune responses. However, trastuzumab also increases tumor expression of PD1/PD-L1, which has been described as a mechanism of resistance to trastuzumab [Park, Y. H. 2011] [Clynes, R. A. 2000] [Loi, S., et al 2014] [Stagg, J., et al 2011] [Loi, S., et al 2013]. These observations led to the hypothesis that using a dual antibody strategy, combining a tumor-targeting antibody with a second antibody that activates the host innate immune system, in combination with standard cytotoxic chemotherapy will improve the therapeutic effects of antibodies against metastatic HER2-expressing tumors.

This hypothesis was tested in a clinical trial recently presented at the San Antonio Breast Cancer Symposium [Loi, S., et al 2017]. In this trial, the combination of pembrolizumab and

trastuzumab was tested in HER2 positive metastatic breast cancer patients who experienced progression during prior trastuzumab-based therapy. The combination was well tolerated without a dose-limiting toxicity (DLT) during dose escalation and notably without a cardiac event (n = 58). In this trastuzumab-resistant population, promising response rates were observed (ORR of 15.2% and DCR of 24%), thus establishing clinical proof of concept for treating patients with a combination of anti-HER2 and anti-PD-1 antibodies.

Although the combination of pembrolizumab, trastuzumab, and chemotherapy has not been studied extensively, 2 investigator-initiated trials were designed to test whether pembrolizumab can be added to current 1L gastric cancer standard-of-care regimen (chemotherapy plus trastuzumab) in HER2 positive patients to improve efficacy in a safe manner. Early results from these 2 studies are promising. Some safety data available from 2 investigator-initiated trials have demonstrated an acceptable safety profile for this combination.

In one investigator-initiated trial conducted at Memorial Sloan Kettering Cancer Center in the US (NCT02954536), pembrolizumab was combined with trastuzumab, oxaliplatin, and either 5-FU or capecitabine. Based on data from 18 patients dosed thus far, the combination has been safe, with no dose-limiting toxicity (DLT) and no drug-related Grade 4 or Grade 5 adverse events (AEs) observed. The only drug-related Grade 3 events reported were hypokalemia (2), anemia (2), alanine aminotransferase increased (2), lymphocyte decrease (1), dehydration (1), nausea (1), rash maculopapular (1), diarrhea (1), and hyponatremia (1). There has been no discontinuation of treatment due to drug-related AEs. In addition, promising anti-cancer activity was observed, with 14/18 patients achieving objective responses (internal Merck data).

In the second investigator-initiated trial, which is ongoing in Korea (NCT02901301), the trial characteristics and regimens are similar except that this trial used cisplatin instead of oxaliplatin. Similar preliminary safety results have been observed. Based on results from 8 patients dosed to date, there have been no DLTs and no drug-related Grade 4 or Grade 5 AEs in this trial; 4 events of Grade 3 neutropenia have been reported. There has been no discontinuation of therapy due to drug-related AEs. Among 8 evaluable patients, 6 patients experienced objective responses (internal Merck data).

While sample size is limited, these early results are promising relative to the 47% ORR observed consistently with current standard of care in HER2 positive gastric cancer patients. It is also reassuring that results appear consistent between 2 separate trials conducted in different regions.

Taken together, accumulating evidence strongly suggests that combining pembrolizumab with current standard-of-care regimen in HER2 positive gastric cancer may improve clinical outcome. Synergistic interaction of pembrolizumab with chemotherapy and trastuzumab presents an opportunity to improve survival and duration of clinical benefit. Given the results of these 2 trials combining trastuzumab with pembrolizumab in HER2 positive cancer, we propose this multicenter, randomized, double-blind Phase 3 study to determine antitumor activity and safety of pembrolizumab and trastuzumab in combination with

chemotherapy [capecitabine and oxaliplatin (CAPOX), or cisplatin and 5-FU (FP)] compared to trastuzumab in combination with chemotherapy in participants with HER2 positive gastric cancer (KEYNOTE-811).

2.2 Background

Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between programmed cell death receptor-1 (PD-1) and programmed cell death ligands 1 and 2 (PD-L1 and PD-L2).

Pembrolizumab was approved in September 2014 by the US FDA for the treatment of melanoma and for non-small cell lung cancer (NSCLC) in October 2015. In June 2016, the European Medicines Agency also approved pembrolizumab for NSCLC. In August 2016, pembrolizumab received FDA approval for head and neck squamous cell carcinoma. In March 2017, pembrolizumab received FDA approval for the treatment of adults and children with relapsed or refractory classical Hodgkin lymphoma, or who have relapsed after 3 or more prior lines of therapy. Recently, pembrolizumab was approved by the FDA for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high or mismatch repair deficient in solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan, and as 3L therapy for PD-L1 positive gastric cancer. For more information, refer to the Investigator's Brochure (IB).

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of cluster of differentiation (CD)8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

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. Programmed cell death-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to 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]. Programmed cell death-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, protein kinase C-theta, and zeta-chain-associated protein kinase, that are involved in the CD3 T-cell signaling cascade [Hunder, N. N., et al 2008] [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].

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

2.2.2 Preclinical and Clinical Studies

Preclinical studies show that monoclonal antibodies against PD1 or CTLA-4 could boost substantially the therapeutic activity of anti-HER2 in immunocompetent mice [Bianchini, G. 2014] [Stagg, J., et al 2011] [Wang, Q., et al 2012]. In particular, Stagg and colleagues report that optimum activity of anti-HER2 treatment needs type I and type II interferons, and interferon γ can also enhance MHC class I and PD-L1 expression on tumor cells [Stagg, J., et al 2011].

Pembrolizumab was recently approved as 3L therapy in PD-L1 positive gastric cancer patients (KN059, Cohort 1). Additionally, the combination of pembrolizumab with cisplatin and 5-FU or capecitabine (KN059, Cohort 2) demonstrated an ORR of 68.0% (95% CI: 46.5%, 85.1%) and a DCR of 72.0% (95% CI: 50.6%, 87.9%). In the KN012 study for heavily treated gastric cancer [Muro, K., et al 2014], the ORR was 30.8% (95% CI: 17.0%, 47.6%) and DCR was 43.6%1 (95% CI (27.8%, 60.4%). Pembrolizumab was generally tolerated with promising efficacy in gastric cancer.

2.2.3 **Ongoing Clinical** Trials of Pembrolizumab in Malignancies

Ongoing clinical studies are being conducted in advanced melanoma, NSCLC, a number of advanced solid tumor indications including gastric and GEJ adenocarcinomas and hematologic malignancies (Table 1). For study details, please refer to the IB.

Table 1 Ongoing Clinical Trials of Pembrolizumab in Gastric Cancer

Study	Phase	Treatment
KN012	1B	Pembrolizumab in PD-L1 positive participants
KN059	2	Pembrolizumab (Cohort 1, 3L treatment), pembrolizumab plus cisplatin and 5-FU or capecitabine (Cohort 2, 1L treatment), pembrolizumab (Cohort 3, 1L treatment)
KN061	3	Pembrolizumab versus paclitaxel, second line treatment
KN062	3	Pembrolizumab versus pembrolizumab plus FP, placebo plus FP, 1L treatment
KN063	3	Pembrolizumab versus paclitaxel, second line treatment
KN585	3	3 cycles of neoadjuvant combination treatment, followed by potentially curative resection, then adjuvant treatment consisting of an additional 3 cycles of combination treatment and 11 cycles of monotherapy

2.2.4 Trastuzumab Plus Chemotherapy

The fluoropyrimidine/platinum combination is a common first-line therapy for metastatic HER2 positive gastric cancer and it is considered "preferred" by the NCCN Gastric Cancer Guideline committee [National Comprehensive Cancer Network 2016]. Platinum/fluoropyrimidine doublet regimens containing cisplatin or oxaliplatin and 5-FU or capecitabine are recognized worldwide as standard first-line chemotherapy regimens for participants with metastatic disease. Most commonly used doublet regimens are capecitabine plus cisplatin (XP), 5-FU plus cisplatin (FP), capecitabine plus oxaliplatin (CAPOX), and 5-FU plus oxaliplatin. There are only a few head to head comparisons between these regimens, and these trials have demonstrated similar efficacy among these doublet chemotherapy regimens in advanced gastric cancer. As such, choices among these regimens are made based on patients' general medical condition and comorbidities in consideration of different toxicity profiles of the regimens. This practice pattern is supported by global consensus guidelines in treatment of advanced gastric cancer which recommend use of any of the doublet of choice discussed above, plus trastuzumab in patients with HER2 positive gastric cancers [National Comprehensive Cancer Network 2016] [Cunningham, D. 2008]. FP and CAPOX have been studied extensively in advanced gastric cancer and are routinely used in clinical practice globally, in combination with trastuzumab in patients with HER2 positive advanced gastric cancers [Ryu, M. H., et al 2015] [Gong, J., et al 2016] [Bang, Y. J., et al 2010]. These 2 regimens are expected to have similar efficacy, and these regimens will allow investigators a choice based on each patient's medical condition.

2.2.5 S-1 (Japan SOX Cohort Only)

S-1 is a combination product containing tegafur, a prodrug of 5-FU, and 2 types of enzyme inhibitors, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1. CDHP increases 5-FU concentration by reversible inhibition of dihydropyrimidine dehydrogenase, an enzyme that degrades 5-FU, while Oxo, densely distributed in gastrointestinal tissues, prevents gastrointestinal toxicity of 5-FU by inhibiting its local activation. S-1 has been developed to enhance therapeutic efficacy in comparison with conventional 5-FU products and also to reverse the resulting increase in adverse drug reactions.

S-1 has been marketed in Japan since 1999. As of January 2017, S-1 is approved for the treatment of gastric cancer, head and neck cancer, colorectal cancer, non-small cell lung cancer, breast cancer, pancreatic cancer and/or biliary tract cancer. It is approved under the trade name of TS-1, S-1, TS-ONE, or Teysuno, in over 45 countries including the European countries (mainly the European Union/European Economic Area) and Asian countries (mainly Japan). To date, cumulative postmarketing exposure to S-1 is estimated to be 1,771,593 patients in Japan since first approval in 1999, approximately 126,964 patients in other Asian countries, and 3966 patients from the European Economic Area, Israel, and Russia since marketing on 14-MAR-2012.

In Japan, combination therapy with fluorinated pyrimidine anticancer agents and platinum containing drugs has been recommended as standard treatment. The Japan Clinical Oncology Group 9912 Study (5-FU versus irinotecan plus cisplatin versus S-1) revealed noninferiority of S-1 monotherapy to continuous IV 5-FU infusion, which was the standard treatment at that time, in terms of OS [Boku, N., et al 2009]. The SPIRITS Study (S-1 versus S-1 plus cisplatin) demonstrated that S-1 plus cisplatin therapy significantly prolonged OS compared with S-1 monotherapy [Koizumi, W., et al 2008]. The ToGA study involving HER2- positive gastric cancer patients showed that trastuzumab added to capecitabine or 5-FU plus cisplatin therapy significantly prolonged OS [Bang, Y. J., et al 2010].

2.2.5.1 Comparison between Cisplatin and Oxaliplatin with S-1

When cisplatin and oxaliplatin are compared, hydration for the prevention of renal toxicity before administration is required for cisplatin; thus, whether or not cisplatin can be replaced with oxaliplatin has been studied. Because the REAL-2 trial (epirubicin plus cisplatin plus 5-FU versus epirubicin plus cisplatin plus capecitabine versus epirubicin plus oxaliplatin plus 5-FU versus epirubicin plus oxaliplatin plus capecitabine) revealed the noninferiority of the oxaliplatin group to the cisplatin group in terms of OS, the efficacy of cisplatin and oxaliplatin is considered to be equivalent [Cunningham, D., et al 2008]. In Japan, the G-SOX study (S-1 plus cisplatin versus S-1 plus oxaliplatin) was conducted to demonstrate the noninferiority of S-1 plus oxaliplatin (SOX) therapy to S-1 plus cisplatin therapy [Yamada, Y., et al 2015]. While the noninferiority of SOX therapy to S-1 plus cisplatin therapy in terms of PFS was shown, the OS result was slightly above the upper limit (1.15) of the noninferiority margin (OS, 13.1 months versus 14.1 months; HR, 0.969 [95% CI, 0.812 to 1.157]). Nonetheless, an ex-post facto (retrospective) analysis using a method to combine 1

subject excluded at the time of the primary analysis revealed that the upper limit of the hazard ratio was below 1.15 (HR, 0.958 [95% CI, 0.803 to 1.142]). In 2009, the Japanese Gastric Cancer Association submitted a request for the expansion of the indication for oxaliplatin for unresectable advanced or recurrent gastric cancer. On the basis of results of REAL-2 trial and G-SOX study, the clinical usefulness of combination therapy with other anticancer agents and oxaliplatin for unresectable advanced or recurrent gastric cancer was determined to be a medically and pharmacologically known fact; thus, it was included in health insurance treatment in September 2014. In addition, the SOPP study (S-1 plus cisplatin versus SOX) conducted in South Korea showed the noninferiority of SOX therapy to S-1 plus cisplatin therapy in terms of PFS [Ryu, M. H., et al 2015]. Consequently, the SOX Q3W regimen is likely to be used as a standard first-line chemotherapy regimen for patients with metastatic gastric cancer.

2.3 Benefit/Risk Assessment

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

The safety and promising efficacy data as described above from multiple studies of pembrolizumab, chemotherapy, and trastuzumab in our target population indicate a strong risk/benefit ratio.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and Informed Consent forms (ICFs).

3. Objectives/Hypotheses and Endpoints

In male and female participants at least 18 years of age with previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To compare PFS between treatment groups. • Hypothesis (H1): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone in terms of PFS per RECIST 1.1 as assessed by blinded independent central review (BICR).	• PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

Objective/Hypothesis	Endpoint
• Objective: To compare OS between treatment groups. • Hypothesis (H2): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone in terms of OS.	• OS: The time from randomization to death due to any cause.
Secondary	
• Objective: To compare ORR between treatment groups. Hypothesis (H3): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone per RECIST 1.1 as assessed by BICR in terms of ORR.	• Objective Response (OR): Complete response (CR) or partial response (PR)
• Objective: To estimate DOR, per RECIST 1.1 as assessed by BICR for each treatment group.	• DOR: The time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first.
• Objective: To assess the safety and tolerability of pembrolizumab in combination with trastuzumab plus chemotherapy by proportion of adverse events (AEs).	• Adverse events • Discontinuation of study treatment due to AEs
Tertiary/Exploratory	
• Objective: To compare the change from baseline in health-related quality of life using the EORTC QLQ-C30 and the EORTC QLQ-STO22 among participants when treated with pembrolizumab in combination with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone.	• EORTC QLQ-C30 and EORTC QLQ-STO22 score.

Objective/Hypothesis	Endpoint
• Objective: To characterize utilities using EuroQoL EQ-5D among participants when treated with pembrolizumab in combination with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone.	• Health utility scores assessed from the EQ-5D-5L
• Objective: To evaluate the genetic and genomic correlates of treatment in pre- and post-treatment blood samples where available.	• Expression of PD-1, PD-L1 and PD-L2 by IHC or ribonucleic acid (RNA) sequencing. • Genetic alterations in PD-1, PD-L1 and PD-L2 on chromosome 9p24.1 by fluorescent in-situ hybridization (FISH).
• Objective: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other biomarkers
• To compare PFS and ORR using modified RECIST 1.1 for immune-based therapeutics (iRECIST), as assessed by the investigator, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	• PFS using iRECIST • OR using iRECIST

4. Study Design

4.1 Overall Design

This is a Phase 3, randomized, placebo-controlled, multi-site, double-blind study in participants diagnosed with previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma.

Approximately 692 participants will be randomized in the Global Cohort in a 1:1 ratio to receive pembrolizumab or placebo each in combination with chemotherapy plus trastuzumab. The investigator has 2 chemotherapy regimen choices, FP or CAPOX, which must be chosen

prior to randomization in the trial. All participants will receive trastuzumab. Participants should continue on the fluoropyrimidine and platinum chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor. Participants will be stratified by geographic region, PD-L1 status, and chemotherapy treatment prior to randomization.

A Japan-specific SOX cohort will enroll and treat an additional approximately 40 participants with trastuzumab, SOX, and either pembrolizumab or placebo. These participants will be stratified by PD-L1 status prior to randomization and their data analyzed separately from the Japanese Global Cohort participants, who will be randomized as part of the Global Cohort and follow the FP or CAPOX treatment regimens to which they are assigned.

Trial treatment in all arms will begin on Day 1 of each 3-week dosing cycle. Trial treatment should begin on the day of randomization or as close as possible to the date on which the participant is allocated/assigned.

Participation in this trial will be dependent upon supplying a tumor tissue specimen. Only participants whose tumors express HER2 positive as determined by the central laboratory will be eligible for randomization in this study. **A newly obtained biopsy of a metastatic site is preferred to archived samples.** Both formalin solution and formalin-fixed, paraffin embedded block specimens are acceptable. If submitting unstained slides, the slides should be freshly cut and received at the testing laboratory within 14 days from site slide section date, otherwise a new specimen will be requested. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 and for other biomarker analyses.

Participants will undergo the first imaging evaluation at Week 6 (+7 days) after participant has been randomized. Subsequently, participants will be evaluated every 6 weeks (42 days ± 7 days), independent of any treatment delays, with radiographic imaging to assess response to treatment using RECIST.1.1. Study treatment will continue until first evidence of Progressive Disease (PD). RECIST 1.1 responses as assessed by BICR will be used as the primary efficacy endpoint; ie, PFS. RECIST 1.1 will be used by the local site for treatment decisions. Treatment should continue until PD has been verified by BICR. Regardless of whether PD is verified, if the investigator considers the participant has progressed, but elects to implement iRECIST (Appendix 9), the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the BICR.

Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The primary and key secondary objectives of the study are described in Section 3.

Treatment will continue until confirmed disease progression, clinical progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, completion

of 35 cycles of treatment with pembrolizumab/placebo, achievement of a CR, or administrative reasons.

Participants who have evidence of PD by imaging and are clinically stable may continue to be treated at the discretion of the investigator. In addition, participants who attain an investigator-determined confirmed CR may consider stopping pembrolizumab/placebo treatment after receiving at least 8 trial administrations in total and at least 2 additional administrations of pembrolizumab/placebo after achieving confirmed CR.

Participants who have achieved SD or better may be eligible for up to 17 additional pembrolizumab cycles if they experience radiographic disease progression while off study treatment according to the criteria in Section 6.7. This "retreatment" is termed the Second Course Phase of this study. Participants are unblinded individually upon disease progression while off study treatment and are able to participate in the Second Course Phase only if they were receiving pembrolizumab originally, and if the study remains open. Response or progression in the Second Course Phase will not count towards the PFS of the primary endpoint in this trial. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of study treatment and the participant still meets the safety parameters listed in the Inclusion/Exclusion criteria (refer to Section 6.7 for further details).

After the end of treatment, each participant will have a 30-day follow-up assessment for AE monitoring (serious adverse events and events of clinical interest (ECI) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier). Participants who discontinue treatment for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be contacted every 12 weeks (±14 days), or more often as needed, for OS until death, withdrawal of consent or the end of the trial, whichever comes first.

Details about interim analyses are in Section 9.7. An independent, external data monitoring committee (DMC) will monitor the safety and efficacy of this study.

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

NOTE: Protocol operational items specific to Japan and Germany are found in Section 10.6, Appendix 6, Country-specific Requirements.

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints in this trial are OS and PFS; the latter is to be assessed by BICR. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real time determination of radiologic progression as determined by central review will be communicated to the site.

Overall survival is the gold standard for a "hard endpoint" in clinical studies in the area of oncology. However, OS results, especially in 1L setting, are often confounded by subsequent therapy. In the US/ EU, gastric cancer is a rare tumor type and most patients have advanced or metastatic disease at the time of diagnosis. Because of the limited number of patients in Western countries and the multiple companies developing this class of drugs for gastric cancer, a high crossover rate is expected for control arm participants who are treated in subsequent trials outside of this protocol.

The largest meta-analysis (36 trials, 10,484 patients) demonstrated that PFS and time to progression were acceptable surrogate markers of OS in patients with advanced gastric cancer [Shitara, K., et al 2012]. As such, improvement in PFS, provided the results are meaningful, provides evidence for clinical benefit. This trial will use a dual endpoint of OS and PFS. RECIST 1.1 by BICR will be used to determine the dates of progression as this methodology is accepted by regulatory authorities.

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility (Section 8.2.1.5). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 8.2.1.6). Immunotherapeutic agents such as 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 patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had PD by RECIST 1.1 but not by the immune-related response criteria

[Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US FDA and the European Medicines Agency [Seymour, L., et al 2017]. 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. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions.

4.2.1.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this trial will be OR and DOR.

Objective Response by RECIST 1.1 criteria as assessed by BICR is considered evidence of efficacy and is a secondary endpoint for this trial. Substantial improvement of OR that is accompanied by duration of response will be considered clinically important surrogate of benefit.

Duration of Response by RECIST 1.1 criteria and assessed by BICR is a commonly accepted endpoint by both regulatory authorities and the oncology community to assess durability of responses to oncology treatments.

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anti-cancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/ SAEs; and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Patient-Reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-STO22 and EuroQoL-5D (EQ-5D) patient-reported outcomes (PROs) are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. The EORTC QLQ-C30, EORTC QLQ-STO-22, and EQ-5D-5L PROs are to be completed by participants at various time points as specified in the SoA.

4.2.1.3.1 EORTC QLQ-C30

EORTC QLQ-C30 is the most widely used cancer specific health related quality of life (QoL) instrument, which contains 30 items and measures 5 functional dimensions (physical,

role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies [Aaronson, N. K., et al 1993].

4.2.1.3.2 EORTC QLQ-STO22

The EORTC QLQ-STO22 is a disease-specific questionnaire developed and validated to address measurements specific to gastric cancer. It is one of multiple disease-specific modules developed by the EORTC QoL Group designed for use in clinical studies, to be administered in addition to the EORTC QLQ-C30 to assess disease-specific treatment measurements. It contains 22 items with symptoms of dysphagia (4 items), pain or discomfort (4 items), reflux symptoms (3 items), eating restrictions (4 items), anxiety (3 items), dry mouth, hair loss, taste, and body image.

4.2.1.3.3 EuroQoL EQ-5D

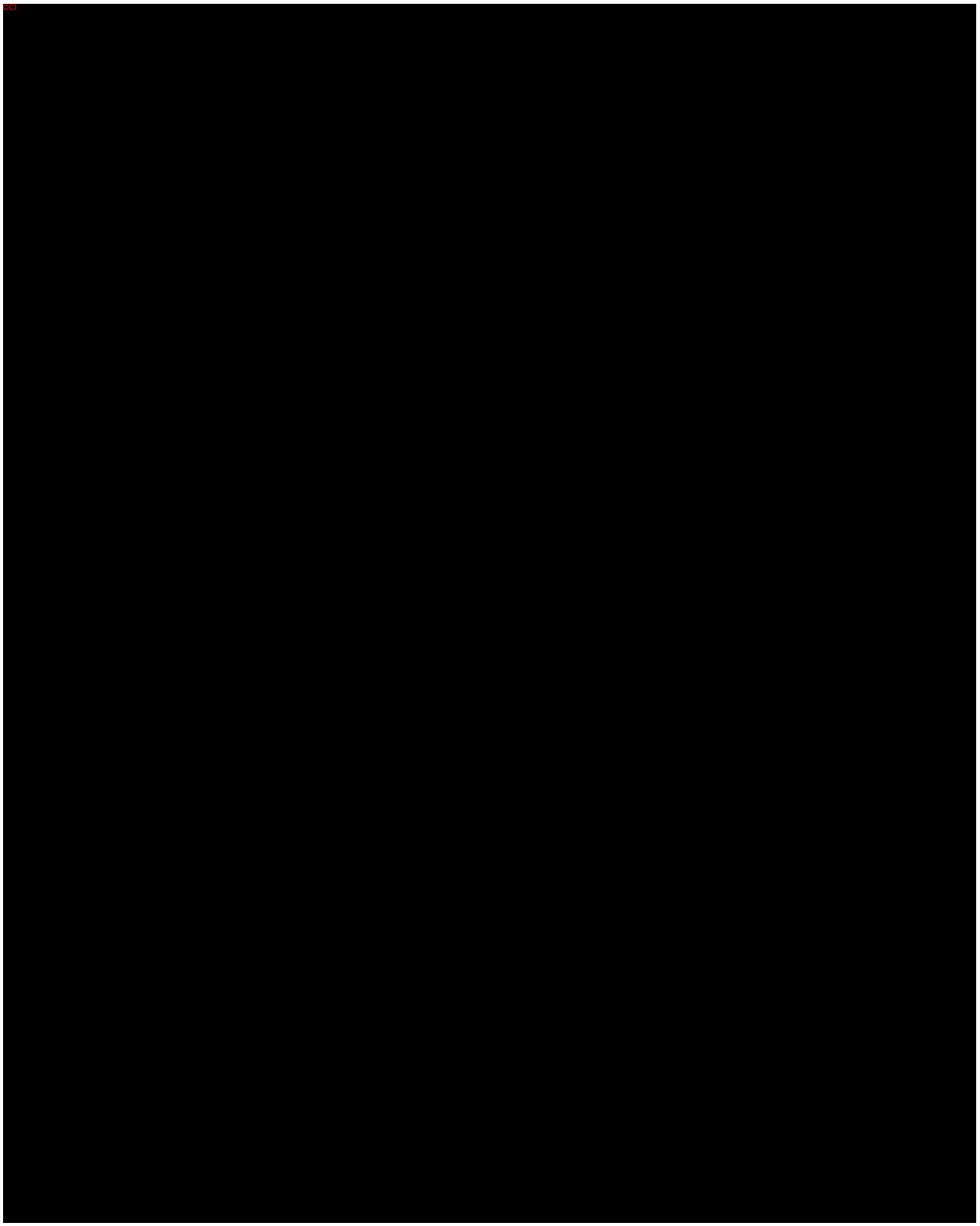
The EuroQoL-5D (EQ-5D) is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. 2001]. The 5 health state dimensions in the EQ-5D include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.4 Pharmacokinetic Endpoints

Blood samples will be obtained to measure pharmacokinetics (PK) of serum pembrolizumab and trastuzumab. Blood samples will also be obtained to measure anti-drug antibodies (ADA) of pembrolizumab and trastuzumab in both arms. Simultaneous PK sampling is required for interpretation of ADA analysis.

4.2.1.5 Planned Exploratory Biomarker Research

[redacted]



CCI

4.2.1.6 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 2.

4.2.2 Rationale for the Use of Comparator/Placebo

4.2.2.1 Rationale of the Use of Placebo

The placebo control is necessary to ensure double blinding since the presence/absence of extra infusions would identify treatment assignment. The placebo control also allows statistical isolation of the true effect associated with pembrolizumab combination therapy from the placebo effect associated with the combination treatment paradigm.

4.2.2.2 Rationale for the Use of Trastuzumab Plus Pembrolizumab in Gastric Cancer

As noted in Section 2.2.4, treatment with trastuzumab results in beneficial, yet limited, clinical improvement for patients with HER2 positive esophagogastric (EG) cancer. Antibody-dependent cell-mediated cytotoxicity by NK cells contributes to the efficacy of trastuzumab [Kohrt, H. E., et al 2012] [Kohrt, H. E., et al 2014]. Junttila et al demonstrated that combining a trastuzumab-based bispecific antibody HER2-TDB with anti-PD-L1 yielded a combination immunotherapy that enhanced tumor growth inhibition, increasing the rates and durability of therapeutic response [Junttila, T. T., et al 2014].

Preclinical studies show that monoclonal antibody against PD-1 boost substantially the efficacy of anti-HER2 treatment. Stagg et al demonstrated synergistic activity of anti-PD-1 and trastuzumab. Combining trastuzumab with anti-PD-1 antibody showed greater tumor regression over trastuzumab alone in positive mouse model.

Data from ongoing KN014-PANACEA trial Phase Ib/II trial evaluating the efficacy of pembrolizumab and trastuzumab in participants with trastuzumab-resistant, HER2-positive, metastatic breast cancer (NCT02129556) indicate that the combination of pembrolizumab and trastuzumab is generally safe and effective.

Two Phase 2 MISP trials have been initiated to evaluate the trastuzumab/pembrolizumab combination plus chemo in HER2+ esophagogastric cancer. In the first study, performed at Memorial Sloan Kettering Cancer Center, no DLT or significant AEs were reported in the first 14 participants enrolled. In the second study, performed in Korea, no DLT or significant AEs were reported in the first 9 participants enrolled (Section 2.1).

Based on these data showing synergistic effect, we hypothesize that enhanced NK cell degranulation and cytotoxicity using PD-1 blockade will result in synergistic activity of pembrolizumab in combination with trastuzumab. We further hypothesize that using a dual antibody strategy, combining a tumor-targeting antibody with a second antibody that activates the host innate immune system, in combination with standard cytotoxic chemotherapy will improve the therapeutic effects of antibodies against metastatic HER2-expressing EG tumors.

4.2.2.3 Rationale for the Use of Trastuzumab, FP and CAPOX in Gastric Cancer

Systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer (NCCN/ESMO guidelines). Platinum/fluoropyrimidine doublet regimens containing cisplatin, 5-FU, or capecitabine are recognized worldwide as standard first-line chemotherapy regimens for participants with metastatic disease. Most commonly used doublet regimens are cisplatin plus capecitabine, FP, CAPOX), and 5-FU plus oxaliplatin. There are only a few head to head comparisons between these regimens, and these trials have demonstrated similar efficacy among these doublet chemotherapy regimens in advanced gastric cancer. As such, choices among these regimens are made based on patients' general medical condition and comorbidities in consideration of different toxicity profile of the regimens. This practice pattern is supported by global consensus guidelines in treatment of advanced gastric cancer which recommend use of any of the doublet of choice discussed

above, plus trastuzumab in patients with HER2 positive gastric cancers [National Comprehensive Cancer Network 2016] [Cunningham, D. 2008]. FP and CAPOX have been studied extensively in advanced gastric cancer and are routinely used in clinical practice globally, in combination with trastuzumab in patients with HER2+ advanced gastric cancers [Ryu, M. H., et al 2015] [Gong, J., et al 2016] [Bang, Y. J., et al 2010]. These 2 regimens are expected to have similar efficacy, and these regimens will allow investigators a choice based on each patient's medical condition.

The current trial will use FP or CAPOX plus trastuzumab as the standard of care backbone regimens. Investigators will have a choice between FP plus trastuzumab and CAPOX plus trastuzumab. As discussed above, these 2 regimens are routinely used in clinical practice globally, in combination with trastuzumab in patients with HER2 positive advanced gastric cancers [Ryu, M. H., et al 2015] [Gong, J., et al 2016] [Bang, Y. J., et al 2010]. These 2 regimens are expected to have similar efficacy, and these regimens will allow investigators choices based on patients' medical conditions. It is important to note that these 2 regimens used in investigators' led trials discussed earlier, and they were safe in combination with pembrolizumab with promising early efficacy results.

The current trial will have a Japan-specific SOX cohort (N=40) that will allow use of SOX. Japanese investigators will use SOX plus trastuzumab as backbone therapy in this cohort. This cohort will be analyzed separately from the main protocol data and will not be included in the analysis of the primary endpoints.

4.3 Justification for Dose

4.3.1 Pembrolizumab Dose

4.3.2 Standard of Care Chemotherapy backbone: FP Dose

Cisplatin (80 mg/m^2 administered on Day 1 of each treatment cycle, Q3W) plus 5-FU (800 mg/m^2/day administered from Day 1 to Day 5 of each treatment cycle Q3W, 120 hours or per local standard).

4.3.3 Standard of Care Chemotherapy backbone: CAPOX Dose

Oxaliplatin 130 mg/m^2 on Day 1 of each cycle (Q3W) over 2 hours plus capecitabine 1000 mg/m^2 bid on Days 1-14 of each cycle (Q3W).

4.3.4 Standard of Care: Trastuzumab Dose

Trastuzumab 8 mg/kg loading dose and then 6 mg/kg maintenance thereafter (Q3W).

4.3.5 SOX Dose (Japan SOX Cohort Only)

S-1 <1.25 m^2 BSA 40 mg bid; 1.25 to <1.5 m^2 BSA 50 mg bid; ≥1.5 m^2 BSA 60 mg bid on Days 1-14 of each cycle (Q3W), plus oxaliplatin 130 mg/m^2 on Day 1 of each cycle (Q3W) over 2 hours.

4.4 Beginning and End of Study Definition

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

4.4.1 Clinical Criteria for Early Study Termination

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

5. Study Population

5.1 Inclusion Criteria

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

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

Type of Participant and Disease Characteristics

1. Male/female participants who are at least 18 years of age on the day of signing the informed consent with histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma.
2. Be HER2-positive defined as either IHC 3+ or IHC 2+ in combination with ISH+ (or FISH), as assessed by central review on primary or metastatic tumor. ISH positivity is defined as a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of signals for CEP17. If the ratio is <2.0 but the HER2 gene copy number is >6 the participant may be considered ISH-positive.
3. Have measurable disease as defined by RECIST 1.1 by scans with IV contrast as determined by the site investigator. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

   Note: The exact same image acquisition and processing parameters should be used throughout the study.

Male participants:

4. A male participant must agree to use an adequate method of contraception as outlined in Appendix 3, for the course of the study through 7 months after the last dose of all study treatments.

Female participants:

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

   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 7 months after the last dose of study treatment.

Informed Consent

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

In Japan, document agreement is necessary for both the participant and their substitute when participants are under 20 years of age.

Other Inclusions

7. Have a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior to the first dose of trial treatment.
8. Have a life expectancy of greater than 6 months.
9. Participants must have a 12-lead electrocardiogram (ECG) and echocardiogram (ECHO) or multigated acquisition (MUGA) scan performed by the investigator or other qualified person to evaluate cardiac function prior to enrollment in the study. Adequate cardiac function will be assessed by:

   a. Left ventricular ejection fraction (LVEF) ≥ 55% as determined by MUGA scan or ECHO. Note: Participants with EF 50 to 54 may still be eligible with discussion with Sponsor AND after consultation with cardiology AND after being medically optimized; and

   b. QT interval calculated according to the Fridericia method (QTcF) value ≤470 msec for males and ≤480 msec for females (mean of 3 measurements corrected for heart rate using Fridericia's formula).
10. Have provided tumor tissue sample deemed adequate for PD-L1 and MSI biomarker analysis. The PD-L1 result must be determined as positive or negative.
11. Have adequate organ function as defined in the following table (Table 2). Specimens must be collected within 10 days prior to the start of study treatment.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine **OR** Measured or calculated[2] creatinine clearance (Glomerular filtration rate can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for participant with creatinine levels >1.5 X institutional ULN **Cisplatin and oxaliplatin product label should be followed for acceptable creatinine clearance rates**
Hepatic	
Total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN **OR** ≤5 X ULN for participants with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.
[1] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.
[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.

5.2 Exclusion Criteria

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

1. Has had previous therapy for locally advanced unresectable or metastatic gastric/GEJ cancer. Participants may have received prior neoadjuvant or adjuvant therapy as long as it was completed at least 6 months prior to randomization and there was no evidence of progression within the timeframe.

2. Has had major surgery, open biopsy or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment.

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

3. Has had radiotherapy within 14 days of randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
4. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
5. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
6. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.
7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.
8. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
9. Has a known history of active tuberculosis (TB; Mycobacterium tuberculosis). No testing for TB is required unless mandated by local health authority.

Note: For Germany and the UK, TB testing is mandatory.

10. Has an active infection requiring systemic therapy.
11. Has poorly controlled diarrhea (eg, watery stool, uncontrollable bowel movement with drugs, Grade ≥ 2 and number of defecations, ≥ 5/day).

12. Accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment. If the participant is receiving diuretic drugs for other reasons, it is acceptable.
13. Has a history or current evidence of any condition (eg, known deficiency of the enzyme dihydropyrimidine dehydrogenase, hearing impairment, etc.), therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator. Participants with a contraindication to standard-of-care therapy should be excluded, ie:
    - Participants with a history of a severe and unexpected reaction to a fluoropyrimidine-containing treatment.
    - Participants with severe dyspnea at rest related to advanced disease stage or oxygen-dependent complications.
    - Participants presenting with clinically significant dehydration should avoid a cisplatin-containing regimen.
    - Participants with hypokalemia, hypomagnesemia, or hypocalcemia.
    - Participants with evidence of neutropenia should not be assigned to an oxaliplatin-containing regimen as recommended by the local package insert.
    - Participants with severe leukopenia should not be assigned to a capecitabine-containing regimen.
14. Has peripheral neuropathy > Grade 1.
15. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.
16. A WOCBP who has a positive urine pregnancy test within 72 hours prior to randomization or treatment allocation (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

    Note: In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.
17. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 7 months after the last dose of trial treatment.
18. Has active or clinically significant cardiac disease including:
    - symptomatic congestive heart failure (CHF) (ie, New York Heart Association Class II or higher)

- history or current evidence of clinically significant cardiac arrhythmia requiring anti-arrhythmic therapy other than beta blockers or digoxin and/or conduction abnormality within 6 months prior to start of study treatment except atrial fibrillation and paroxysmal supraventricular tachycardia
- active coronary artery disease
- unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization
- myocardial infarction within 6 months before randomization

19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). No testing for HIV is required unless mandated by local health authority.

Note: For Germany and the UK, HIV testing is mandatory.

20. Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. No testing for hepatitis B and hepatitis C is required unless mandated by local health authority.

Note: For Germany and the UK, hepatitis B and C testing is mandatory.

21. Has severe hypersensitivity (≥Grade 3) to pembrolizumab, trastuzumab, study chemotherapy agents and/or to any excipients, murine proteins, or platinum-containing products.
22. Has had an allogeneic tissue/solid organ transplant.

Prior/Concomitant Therapy

23. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137)
24. Has received a live vaccine within 30 days prior to the first dose of study treatment.

    Note: 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*, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

25. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to 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 after the last dose of the previous investigational agent.

5.3 Lifestyle Considerations

No restrictions are necessary.

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are necessary.

5.3.3 Activity Restrictions

No restrictions are necessary.

5.3.4 Photosensitivity

Investigators are advised to counsel participants assigned to receive capecitabine or 5-FU about the risk of photosensitivity and to take sun protection measures accordingly.

5.3.5 Contraception

Pembrolizumab and other study medications may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 3) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 7 months after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.6 Pregnancy

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

must be informed immediately and the pregnancy must be reported to the Sponsor. All pregnancies must be reported and followed as described in Section 8.4.

5.3.7 Use in Nursing Women

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6. 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 as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Treatments Administered

The treatments to be used in this study are outlined in Table 3.

Table 3 Study Treatments

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)**	Dosage Level(s)	Route of Administration	Use	IMP/NIMP	Sourcing
Pembrolizumab/Placebo							
Pembrolizumab (MK-3475)	Vial	25 mg/mL vial	200 mg on Day 1 of each cycle (Q3W)	IV infusion via infusion pump	Experimental	IMP	Provided centrally by the Sponsor
Placebo	Solution for infusion, refer to the Pharmacy Manual	N/A	On Day 1 of each cycle (Q3W)	IV infusion via infusion pump	Placebo	IMP	Provided locally by the study site, subsidiary, or designee
FP							
Cisplatin*	Vial	1 mg/mL vial 20 mg vial	80 mg/m^2 on Day 1 of each cycle (Q3W)	IV infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
5-FU	Vial	25 mg/mL vial 50 mg/mL vial	800 mg/m^2/day continuous on Days 1-5 of each cycle (Q3W) (120 hours, or per local standard)	IV infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
CAPOX							
Oxaliplatin***	Vial	5 mg/mL vial 50 mg vial	130 mg/m ^{2} on Day 1 of each cycle (Q3W) over 2 hours	IV infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Capecitabine	Tablet	150 mg tablet 500 mg tablet	1000 mg/m^2 bid on Days 1-14 of each cycle (Q3W)	Oral	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)**	Dosage Level(s)	Route of Administration	Use	IMP/NIMP	Sourcing
SOX (Japan only)							
S-1	Capsule	20 mg capsule 25 mg capsule	<1.25 m^2 BSA 40 mg bid on Days 1-14 of each cycle (Q3W). 1.25 to <1.5 m^2 BSA 50 mg bid on Days 1-14 of each cycle (Q3W). ≥1.5 m^2 BSA 60 mg bid on Days 1-14 of each cycle (Q3W).	Oral	Comparator regimen and combination agent	NIMP	Provided locally by the study site, subsidiary, or designee
Oxaliplatin	Vial	5 mg/mL vial 50 mg vial	130 mg/m^2 on Day 1 of each cycle (Q3W) over 2 hours	IV infusion	Comparator regimen and combination agent	NIMP	Provided locally by the study site, subsidiary, or designee
Trastuzumab							
Trastuzumab	Vial	60 mg vial (Japan only) 150 mg vial 440 mg vial 600 mg vial	8 mg/kg loading dose, and then 6 mg/kg maintenance thereafter (Q3W)	IV infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) are based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Pembrolizumab/trastuzumab will be administered until disease progression or other withdrawal criteria are met.

* Duration of cisplatin treatment may be capped at 6 cycles as per local country guidelines; however, treatment with 5-FU may continue per protocol.

** The strength of treatment may vary depending on the source. The table captures the current available strengths but could vary depending on availability.

*** CAPOX: duration of oxaliplatin may be capped at 6 or 8 cycles as per local country guidelines; however, treatment with capecitabine may continue per protocol.

All supplies indicated in Table 3 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 where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

The rationale for selection of dose of pembrolizumab to be used in this trial is provided in Section 4.3.1. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Dose preparation must be done by separate unblinded trial personnel. Dose administration must be done by blinded trial personnel.

Preparation of trastuzumab, cisplatin, 5-FU, and capecitabine should follow the local product label. The body surface area (BSA) in m^2 should be calculated per local guidance.

6.2.2 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 (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

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

6.3.1.1 Stratification

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

1. Geographic region (Global Cohort only) –
    - Europe/Israel/North America/Australia
    - Asia
    - Rest of the World (including South America)
2. PD-L1 status (positive versus negative)
3. Chemotherapy regimen (FP or CAPOX)

Japan-specific SOX cohort

1. PD-L1 status (positive versus negative)

6.3.2 Blinding

A double-blinding technique will be used. Study medications will be prepared and/or dispensed according to the specifications in the pharmacy manual. The participant and the investigator who is involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Treatment Compliance

Interruptions from the protocol-specified treatment plan for greater than 12 weeks between pembrolizumab doses for non-study medication-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

For those medications taken at home, the site will validate compliance with study medication at each site visit according to their standard operating procedure.

6.5 Concomitant Therapy

6.5.1 Specific Restrictions

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing 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 Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

Listed below are concomitant therapies prohibited during the course of the study:

- Anti-cancer immunotherapy, chemotherapy, or biological therapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Palliative radiation therapy to a symptomatic lesion (eg, bony metastasis), or to the brain may be permitted after consultation with the Sponsor.
- Live vaccines within 30 days prior to the first dose of study treatment, while participating in the study, for at least 90 days after the last study treatment, and per local standard of care. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not permitted.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. Inhaled or topical steroids are allowed, and systemic steroids at doses ≤ 10 mg/day prednisone or equivalent are allowed.
- For participants receiving 5-FU, S-1 or capecitabine:
  - Brivudine, Sorivudine analogs, and other inhibitors of the enzyme dihydropyrimidine dehydrogenase
- For participants receiving cisplatin:
  - Phenytoin should not be started with cisplatin therapy.
- Pre-cisplatin treatment with corticosteroids per NCCN or institutional guideline is permitted.

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

Concomitant Medications to be used with caution

- Cimetidine, metronidazole and interferons may increase levels of 5-FU.

- Participants who are taking phenytoin in conjunction with 5-FU should be examined regularly due to a potential elevation in phenytoin plasma levels. Hepatotoxic effects (rise in alkaline phosphatase, transaminase, or bilirubin levels) are commonly observed under the treatment with 5-FU and levamisole.

For participants receiving cisplatin:

- Concomitant administration of nephrotoxic (eg, cephalosporins, aminoglycosides, Amphotericin B or contrast media) or ototoxic (eg, aminoglycosides) medicinal products will potentiate the toxic effect of cisplatin.

For participants receiving oxaliplatin:

- Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored.
- Caution is advised if medicinal products associated with rhabdomyolysis are administered concomitantly with oxaliplatin.

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

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and ECIs as defined in Section 8.4.7.

6.5.2 Rescue Medications and Supportive Care

6.5.2.1 Supportive Care Guidelines for Cisplatin

Participants should be well-hydrated while taking cisplatin.

Prevention and/or treatment of nausea and vomiting should be managed with:

1. IV EMEND (fosaprepitant) 150 mg IV or oral EMEND (aprepitant) 3-day pack 125 mg Day 1, 80 mg Day 2, 80 mg Day 3

2. Plus Aloxi (palonosetron) 0.25 mg IV

Nausea may also be managed with:

1. Zofran (ondansetron) 8 mg twice a day

2. Or Compazine (prochlorperazine) 10 mg 3-4 times per day

Additionally, use of steroids for cisplatin associated anti-emetic support is allowed and is to follow the NCCN or institutional guidelines. However, caution must be exercised to prevent the overuse of steroids.

Please refer to the product label or local standards of care for additional cisplatin supportive measures.

6.5.2.2 Supportive Care Guidelines for 5-FU

Please refer to the product label or local standards of care for 5-FU supportive measures.

6.5.2.3 Supportive Care Guidelines for Capecitabine

Please refer to the product label or local standards of care for capecitabine supportive measures.

6.5.2.4 Supportive Care Guidelines for Oxaliplatin

Please refer to the product label or local standards of care for oxaliplatin supportive measures.

6.5.2.5 Supportive Care Guidelines for S-1 (Japan SOX Cohort Only)

Please refer to the product label or local standards of care for S-1 supportive measures.

6.5.2.6 Supportive Care Guidelines for Trastuzumab

Please refer to the product label or local standards of care for trastuzumab supportive measures.

6.5.3 Curative Surgery

In general, surgical resection in participants who have metastatic disease is not encouraged, except in exceptional cases as the benefit of surgery is unknown in this setting. However, if it is determined that participants are eligible for a potential curative surgical resection, in the event of strong tumor response, please contact the Sponsor for guidance. Participants who have curative surgery while on study will be defined as participants who have had tumor resection and postresection imaging restaging to include at minimum contrasted CT chest, abdomen, pelvis, plus imaging of any part of the body previously known to have tumor, all of which must show no residual disease in the participant. Contrasted MRI or PET CT may be allowed, if appropriate, for restaging imaging. Participants who have surgery should continue imaging as detailed in the SoA (Section 1.3) until PD, or they otherwise meet the discontinuation criteria (Section 8.2.1.2 and Section 8.2.1.3).

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Selection (Preparation)

The rationale for selection of dose of pembrolizumab to be used in this trial is provided in Section 4.3.1. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Preparation of oxaliplatin, cisplatin, 5-FU, capecitabine, and S-1 should follow the local product label. The BSA in m^2 should be calculated per local guidance. The dose of chemotherapy and trastuzumab should be recalculated for fluctuation of body weight ≥10% at the beginning of a cycle only. For weight fluctuation <10%, recalculation may be done at the discretion of the investigator. When recalculating, BSA in m^2 should be calculated per local guidance.

6.6.2 Dose Modification and Toxicity Management

The investigator may attribute each toxicity event to oxaliplatin, cisplatin, S-1 (Japan only), 5-FU, capecitabine, trastuzumab, or pembrolizumab alone and use a stepwise dose reduction according to Table 4 through Table 14. Dose modification should be performed with the following taken into consideration.

- Treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to the guideline for restarting each study treatment.
- Pembrolizumab and trastuzumab dose reductions are not permitted. Pembrolizumab or trastuzumab treatment may be interrupted or discontinued due to toxicity.
- If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated.
- Participants can have a maximum of 2 dose modifications for toxicities (if applicable) to 5-FU, cisplatin, capecitabine, and S-1 (Japan only), a maximum of 3 dose modifications to oxaliplatin throughout the course of the study. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).
- Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to on one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs may be considered to be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, chemotherapy may be considered to be reduced, interrupted or discontinued. Pembrolizumab and/or trastuzumab should be interrupted or discontinued according to the recommended dose modifications.
- Both groups may have trastuzumab and/or the chemotherapy discontinued and continue to receive pembrolizumab/placebo.

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 4 through Table 14. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

If toxicity is not otherwise specified, investigators should refer to the label or local guidelines for oxaliplatin, cisplatin, 5-FU, capecitabine, trastuzumab, and S-1 (Japan only) for dose adjustments.

In addition, participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures are included in Table 4 (pembrolizumab) and Section 6.5.2.

6.6.3 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

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

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated With Pembrolizumab

General instructions:

Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
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.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or increased Bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 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	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
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[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
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 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome and encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE=adverse event; ALT=alanine aminotransferase; AST= aspartate aminotransferase; CTCAE= Common Toxicity Criteria for Adverse Events; GI=gastrointestinal; irAE=immune related adverse event; IV=intravenous; T1DM=Type 1 diabetes mellitus.

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

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

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

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

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**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 h (±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).

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

CTCAE=Common Toxicity Criteria for Adverse Events; IV=intravenous; NCI= National Cancer Institute; NSAID=non-steroidal anti-inflammatory drug; po=per OS (orally).
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v4.0 at http://ctep.cancer.gov.

Other allowed dose interruption for pembrolizumab

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

6.6.4 Dose Modification and Toxicity Management for CAPOX, FP and SOX

Please refer to criteria for dose modification and discontinuation in Table 6, Table 7, and Table 8 for CAPOX; Table 9, Table 10, and Table 11 for FP; and Table 12, Table 13, and Table 14 for SOX. See the agents' respective package inserts for more details.

Dose delays and treatment restarts will be made at the discretion of the site investigator according to institutional guidelines or local standard practice. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated.

Oxaliplatin administration must be discontinued in the case of QT/QTc interval prolongation >500 msec. Continuous ECG (telemetry) monitoring in a hospital setting under the care of a cardiologist will be required in the case of QT/QTc prolongation >500 msec.

If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

If a toxicity is not otherwise specified, investigators should refer to the label or local guidelines for dose adjustments.

6.6.4.1 CAPOX Dose Modification

Table 6 Recommended Dose Modification Guidelines for CAPOX Drug-related Adverse Events

	Dose Level 0	**Dose Level 1**	**Dose Level 2**	**Dose Level 3**	**Dose Level 4**
Oxaliplatin	130 mg/m^2	100 mg/m^2	75 mg/m^2	50 mg/m^2	Discontinue
Capecitabine	1000 mg/m^2 BID	750 mg/m^2 BID	500 mg/m^2 BID	Discontinue	Discontinue

Table 7 Recommended Dose Modification Guidelines for Oxaliplatin Drug-related Adverse Events

Category	Toxicity	Hold Oxaliplatin Treatment for Grade	Timing for Restarting Oxaliplatin Treatment	Dose for Restarting Oxaliplatin Treatment	Discontinue Oxaliplatin
Hematologic[1]	Neutropenia[5]	2-3[2]	Neutrophil count resolves to ≥1500/mm^3	No Reduction If the criteria for starting the course are not met at Day 22, reduce by 1 DL.	If >3 DL reductions exceeded
		4[2]	Neutrophil count resolves to ≥1500/mm^3	Reduce by 1 DL	If >3 DL reductions exceeded
	Febrile neutropenia	3-4[2]	Toxicity resolves	Reduce by 1 DL	If >3 DL reductions exceeded
	Thrombocytopenia	3-4[2]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL[3]	If >3 DL reductions exceeded
Non-hematologic[1]	Creatinine increased	≥1.5 mg/dL[2]	<1.5 mg/dL	No reduction	If >3 DL reductions exceeded
	Peripheral sensory neuropathy[4]	3-4[2]	Grade 0-2	Reduce by 1 DL	If >3 DL reductions exceeded
	All other non-hematologic toxicities[1]	3-4[2]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >3 DL reductions exceeded
	Laboratory Adverse Events[6]	3-4[2]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >3 DL reductions exceeded

DL = Dose Level.

[1] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
[2] *Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.*
[3] Dose reduction at Grade 3 is at the discretion of the investigator but not required.
[4] Administration may be interrupted or reduced at the discretion of the investigator.
[5] See the package insert of each G-CSF drugs for administration of G-CSF for neutropenia.
[6] Allow continuous treatment for non-clinical significant lab AE, such as low MG, CA, or K, that is asymptomatic and deemed to be safe by the investigator.

Table 8 Recommended Dose Modification Guidelines for Capecitabine Drug-related Adverse Events

Category	Toxicity	Hold Capecitabine Treatment for Grade	Timing for Restarting Capecitabine Treatment	Dose for Restarting Capecitabine Treatment	Discontinuation of Capecitabine
Hematologic	Neutropenia	2-3[1]	Neutrophil count resolves to >1500/mm^3	No Reduction *consider G-CSF	Toxicity does not resolve within 4-5 weeks of last administration or if >2 DL reductions exceeded
		4[1]	Neutrophil count resolves to >1500/mm^3	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 4-5 weeks of last administration or if >2 DL reductions exceeded
	Febrile Neutropenia	2-3[1]	Toxicity resolves	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last administration or if >2 DL reductions exceeded
		4[1]	n/a	Discontinue	Permanently discontinue
	Thrombocytopenia	2-4[1]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last administration or if >2 DL reductions exceeded
Non-hematologic	Diarrhea, Mucositis, or Hand-foot syndrome	2-3	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last administration or if >2 DL reductions exceeded
		4	N/A	Discontinue	Permanently discontinue
	All other non-hematologic toxicities	2-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last administration or if >2 DL reductions exceeded
	Laboratory Adverse Events[2]	4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last administration or if >2 DL reductions exceeded

DL = Dose Level

[1] *Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug related AE.*

[2] Allow continuous treatment for non-clinical significant lab AE, such as low MG, CA, or K, that is asymptomatic and deemed to be safe by the investigator.

6.6.4.2 FP Dose Modification

Table 9 Recommended Dose Modification Guidelines for FP Drug-related Adverse Events

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	80 mg/m^2	60 mg/m^2	40 mg/m^2	Discontinue
5-FU	800 mg/ m^2	600 mg/m^2	400 mg/m^2	Discontinue

Table 10 Recommended Dose Modification Guidelines for Cisplatin Drug-related Adverse Events

Category	Toxicity	Hold Cisplatin Treatment for Grade	Timing for Restarting Cisplatin Treatment	Dose for Restarting Cisplatin Treatment	Discontinue Cisplatin
Hematologic[3]	Neutropenia	3[1]	Neutrophil count resolves to >1000/mm^3	No Reduction *consider G-CSF	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
		4[1]	Neutrophil count resolves to >1000/mm^3	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
	Febrile Neutropenia	3[1]	Toxicity resolves	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
		4[1]	n/a	Discontinue	Permanently discontinue cisplatin
	Thrombocytopenia	1-4[1]	Platelet count resolves to ≥100,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded

Category	Toxicity	Hold Cisplatin Treatment for Grade	Timing for Restarting Cisplatin Treatment	Dose for Restarting Cisplatin Treatment	Discontinue Cisplatin
Non-hematologic	Creatinine Increased	2	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
		3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
	Ototoxicity	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
	Sensory neuropathy	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
	Laboratory Adverse Events[4]	4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded

DL = Dose Level.

[1] *Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.*

[2] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held and did not recover to Grade 0-1 within 12 weeks of the last dose.

[3] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

[4] Allow continuous treatment for non-clinical significant lab AE, such as low MG, CA, or K, that is asymptomatic and deemed to be safe by the investigator.

Table 11 Recommended Dose Modification Guidelines for 5-FU Drug-related Adverse Events

Category	Toxicity	Hold 5-FU Treatment for Grade	Timing for Restarting 5-FU Treatment	Dose for Restarting 5-FU Treatment	Discontinue 5-FU
Hematologic[3]	Neutropenia	3[1]	Neutrophil count resolves to >1000/mm^3	No Reduction *consider G-CSF	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
		4[1]	Neutrophil count resolves to >1000/mm^3	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
	Febrile Neutropenia	3[1]	Toxicity resolves	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
		4[1]	n/a	Discontinue	Permanently discontinue
	Thrombocytopenia	3-4[1]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded

Category	Toxicity	Hold 5-FU Treatment for Grade	Timing for Restarting 5-FU Treatment	Dose for Restarting 5-FU Treatment	Discontinue 5-FU
Non-hematologic	Diarrhea, Mucositis, or Hand-foot syndrome	2-3	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
		4	NA	Discontinue	Permanently discontinue
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
	Laboratory Adverse Events[4]	4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded

DL = Dose Level.

[1]*Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.*

[2]Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held, and did not recover to Grade 0-1 within 12 weeks of the last dose.

[3]Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

[4]Allow continuous treatment for non-clinical significant lab AE, such as low MG, CA, or K, that is asymptomatic and deemed to be safe by the investigator.

6.6.4.3 SOX Dose Modification (Japan SOX Cohort Only)

Table 12 Recommended Dose Modification Guidelines for SOX Drug-related Adverse Events (Japan SOX Cohort Only)

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3	Dose Level -4
Oxaliplatin	130 mg/m^2	100 mg/m^2	75 mg/m^2	50 mg/m^2	Discontinue
S-1	60 mg/dose 50 mg/dose 40 mg/dose	50 mg/dose 40 mg/dose Discontinue	40 mg/dose Discontinue Discontinue	Discontinue Discontinue Discontinue	Discontinue Discontinue Discontinue

Table 13 Recommended Dose Modification Guidelines for Oxaliplatin Drug-related Adverse Events

Category	Toxicity	Hold Oxaliplatin Treatment for Grade	Timing for Restarting Oxaliplatin Treatment	Dose for Restarting Oxaliplatin Treatment	Discontinue Oxaliplatin
Hematologic[1]	Neutropenia[5]	2-3[2]	Neutrophil count resolves to ≥1500/mm^3	No Reduction If the criteria for starting the course are not met at Day 22, reduce by 1 DL.	If >3 DL reductions exceeded
		4[2]	Neutrophil count resolves to ≥1500/mm^3	Reduce by 1 DL	If >3 DL reductions exceeded
	Febrile neutropenia	3-4[2]	Toxicity resolves	Reduce by 1 DL	If >3 DL reductions exceeded
	Thrombocytopenia	3-4[2]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL[3]	If >3 DL reductions exceeded

Category	Toxicity	Hold Oxaliplatin Treatment for Grade	Timing for Restarting Oxaliplatin Treatment	Dose for Restarting Oxaliplatin Treatment	Discontinue Oxaliplatin
Non-hematologic	Creatinine increased	≥1.5 mg/dL[2]	<1.5 mg/dL	No reduction	If >3 DL reductions exceeded
	Peripheral sensory neuropathy[4]	3-4[2]	Toxicity resolves to Grade 0-2	Reduce by 1 DL	If >3 DL reductions exceeded
	All other non-hematologic toxicities[1]	3-4[2]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >3 DL reductions exceeded
	Laboratory Adverse Events[6]	4[2]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >3 DL reductions exceeded

DL = Dose Level

[1] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

[2] *Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.*

[3] Dose reduction at Grade 3 is at the discretion of the investigator but not required.

[4] Administration may be interrupted or reduced at the discretion of the investigator.

[5] See the package insert of each G-CSF drugs for administration of G-CSF for neutropenia.

[6] Allow continuous treatment for non-clinical significant lab AE, such as low MG, CA, or K, that is asymptomatic and deemed to be safe by the investigator.

Table 14 Recommended Dose Modification Guidelines for S-1 Drug-related Adverse Events

Category	Toxicity	Hold S-1 Treatment for Grade	Timing for Restarting S-1 Treatment	Dose for Restarting S-1 Treatment	Discontinue S-1
Hematologic[1]	Neutropenia[3]	3[2]	Neutrophil count resolves to ≥1500/mm^3	No Reduction If the criteria for starting the course are not met at Day 22, reduce by 1 DL.	If >2 DL reductions exceeded
		4[2]	Neutrophil count resolves to ≥1500/mm^3	Reduce by 1 DL	If >2 DL reductions exceeded
	Febrile neutropenia	3-4[2]	Toxicity resolves	Reduce by 1 DL	If >2 DL reductions exceeded
	Thrombocytopenia	3-4[2]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL	If >2 DL reductions exceeded

Category	Toxicity	Hold S-1 Treatment for Grade	Timing for Restarting S-1 Treatment	Dose for Restarting S-1 Treatment	Discontinue S-1
Non-hematologic	Diarrhea, Mucositis, or Hand and foot syndrome	2-4[2]	Grade 0-1	Reduce by 1 DL	If >2 DL reductions exceeded
	Creatinine increased	≥1.5 mg/dL[2]	<1.5 mg/dL	No Reduction	If >2 DL reductions exceeded
	All other non-hematologic toxicities[1]	3-4[2]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >2 DL reductions exceeded
	Laboratory Adverse Events[4]	3-4[2]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >2 DL reductions exceeded

DL = Dose Level.

[1] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

[2] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug related AE.

[3] See the package insert of each G-CSF drugs for administration of G-CSF for neutropenia.

[4] Allow continuous treatment for non-clinical significant lab AE, such as low MG, CA, or K, that is asymptomatic and deemed to be safe by the investigator.

6.6.5 Dose Modification and Toxicity Management for Trastuzumab

Caution should be exercised when treating participants with clinically significant cardiovascular disease such as preexisting coronary artery disease or CHF. Participants with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia should not be enrolled in clinical trials with trastuzumab. Trastuzumab should be discontinued in the event of any Grade 3 or 4 events consistent with CHF.

There will be no dose modifications of trastuzumab. Trastuzumab dose delays are permitted for Grade 3/4 clinical toxicity or at investigator discretion. Dose delays are not required for laboratory abnormalities unless associated with clinical symptoms. Omitted doses of trastuzumab are not replaced or restored; instead, the participant should resume the planned treatment cycles. Participants who develop signs and symptoms of CHF should have trastuzumab held and should receive treatment for CHF. Participants with an asymptomatic absolute decrease in LVEF of ≥16 percentage points or an absolute decrease in LVEF of ≥10 percentage points to below the lower limit of normal should have trastuzumab held as outlined below.

Congestive Heart Failure and Other Cardiac Dysfunction

All participants must have a baseline evaluation of cardiac function, including a measurement of LVEF by ECHO, prior to entry into the study. If an ECHO cannot be performed or is technically limited, a MUGA scan can alternatively be performed. Only participants with normal LVEF (≥55%) should be entered into this study. All participants will undergo regular cardiac monitoring throughout the study, including at baseline and repeated at Cycles 3 and 5 and every 4 cycles starting from Cycle 9. During the course of trastuzumab therapy, participants should be monitored for signs and symptoms of CHF (ie, dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). Participants who develop signs or symptoms of CHF will be further evaluated with a repeat LVEF assessment using the same method selected at baseline (either ECHO or MUGA) if possible.

Management of Symptomatic Cardiac Changes

Participants who develop signs and symptoms of CHF should have trastuzumab held and should receive treatment for CHF as recommended by the ACC/AHA (eg, angiotensin converting enzyme inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics, and cardiac glycosides, as needed) with referral to cardiology for consultation.

If the symptoms of CHF resolve with treatment, and/or cardiac function improves to baseline, reinitiating of trastuzumab can be considered at the discretion of the investigator, after discussion with the participant concerning the risks and benefits of continued therapy and in consultation with a cardiologist. If the participant is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction or heart failure. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO) will resume as regularly scheduled. Additional LVEF

assessments prior to the next regularly scheduled LVEF measurement may be performed at the investigator's discretion.

Management of Asymptomatic Decreases in LVEF

Trastuzumab can be continued in participants experiencing an asymptomatic absolute decrease in LVEF of <16 percentage points from baseline, when the ejection fraction remains within the imaging center's range of normal limits. Repeat measures of LVEF should be obtained using the methodology selected at baseline if possible. Close follow-up of such participants is recommended. Participants with an asymptomatic absolute decrease in LVEF of ≥16 percentage points or an absolute decrease in LVEF of ≥10 percentage points to below the lower limit of normal should have trastuzumab held. Referral to cardiology should be considered for evaluation and management of left ventricular systolic dysfunction with adherence to ACC/AHA guidelines. In light of the variability inherent in the assessment of ejection fraction, consideration should be given to repeating the study within 4-7 days to confirm an observed decline. Repeat measures of LVEF should be obtained using the same methodology selected at baseline if possible, but at the discretion of the investigator or consulting cardiologist. If trastuzumab has been held for an asymptomatic decline in LVEF, a repeat measure of LVEF will be obtained within 1 month to evaluate for recovery of LVEF. If LVEF does not improve after repeat assessment within 1 month, the participant should be monitored with monthly or as clinically indicated ECHOs/MUGAs until LVEF is improved.

If cardiac function improves and LVEF no longer meets "hold" criteria as defined above, trastuzumab may be restarted. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO), using the optimal methodology as determined by the investigator or consulting cardiologist, will resume per the standard schedule. Additional LVEF assessments prior to the next regularly scheduled LVEF measurement may be performed at the investigator's discretion. If the participant is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction even in the setting of an asymptomatic LVEF decline and reinitiating of trastuzumab can be considered at the discretion of the investigator after consultation with a cardiologist and discussion with the participant concerning the risks and benefits of continued therapy.

See the trastuzumab package insert for more details.

6.7 Second Course Phase (Retreatment Period)

All participants who have received pembrolizumab and stop trial treatment with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping trial treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this trial and is only available if the trial remains open and the participant meets the following conditions:

Condition #1

Either

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
  - Was treated with at least 8 cycles of pembrolizumab before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

Or

- Had SD, PR, or CR and stopped trial treatment after completion of 35 administrations of pembrolizumab for reasons other than disease progression or intolerability

AND

Condition #2

- Experienced an investigator-determined radiographic disease progression after stopping initial treatment, and
  - Completed first course of trial treatment, stopped trial treatment with SD or better, and upon disease progression were unblinded and found to have received pembrolizumab, and
  - No new anticancer treatment was administered after the last dose of trial treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The trial is ongoing.

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

6.8 Treatment After the End of the Study

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

6.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IRT) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

7. Discontinuation of Study Treatment and Participant Withdrawal

7.1 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 1.3 and Section 8.10.3.

Participants may discontinue study treatment at any time for any reason or be discontinued 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 8.10.3.

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.
- Unacceptable AEs.
- The participant interrupts study treatment administration for more than 12 consecutive weeks unless Sponsor approval to continue is received.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Confirmed radiographic disease progression outlined in Section 8.2 (exception if the Sponsor approves treatment continuation).

- Noncompliance with study treatment or procedure requirements.
- Recurrent Grade 2 pneumonitis.
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab/placebo and at least 80% of the planned doses of the other study treatments beyond the date when the initial CR was declared. These participants may be eligible for Second Course treatment described in Section 6.7.
- Completion of 35 treatments (approximately 2 years) with pembrolizumab.
  Note: The number of treatments is calculated starting with the first dose.
- The participant has a confirmed positive serum pregnancy test.

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

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for 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 study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C, 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 at each treatment cycle/visit will be approximately 6.0 mL-51.0 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

The participant or his/her legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

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

8.1.4 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 this study will be recorded separately and not listed as medical history.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

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

8.1.5.3 Disease Status and Prior Cancer Treatment History

The investigator or qualified designee will also review the participant's current disease status. They will also review all prior anti-cancer treatments including systemic treatments, radiation, and surgeries.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 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 8.10.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

The investigator must decide the choice of intervention and provide the rationale prior to randomization.

8.1.7.1 Treatment Eligibility Assessment

The treatment eligibility assessment is included in this study to document investigator assessment of participant suitability for potential treatment with study interventions other than pembrolizumab and the rationale. These data may be required to support reimbursement efforts for pembrolizumab.

The investigator must provide rationale to document the choice of study interventions prior to randomization.

8.1.8 Treatment Administration

Administration of study medication will be performed according to the specifications in the Pharmacy Manual.

Study Treatment should begin within 3 days of randomization.

8.1.8.1 Timing of Dose Administration

Trial treatment in all arms will begin on Day 1 of each 3-week dosing cycle after all procedures/assessments have been completed as detailed in the SoA (Section 1.3). Trial treatments may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments may be administered on an outpatient basis.

Treatments will be administered in the order presented below:

- Pembrolizumab or placebo infusion is administered first, followed by trastuzumab infusion, then cisplatin or oxaliplatin infusion, and then 5-FU infusion, capecitabine, or S-1 (Japan Only).

Treatment may continue until confirmed disease progression, clinical progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant receives 35 administrations (approximately 2 years) of study medication, achievement of a CR, or administrative reasons requiring cessation of treatment.

Note: Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (ie, elective surgery, unrelated medical events, participant vacation, and holidays) not related to study therapy. Participants should be placed back on study therapy as soon as clinically appropriate per the investigator, and not exceeding 3 weeks from the interrupted dosing. Day 1 of subsequent cycles should be adjusted accordingly to adhere to Q3W dosing schedule. Discuss with the Sponsor if participants cannot restart study medication within 3 weeks. The reason for interruption should be documented in the participant's study record.

8.1.8.2 Pembrolizumab and Placebo

Pembrolizumab or placebo must be administered on Day 1 of each 3-week cycle for up to 35 cycles after all procedures/assessments have been completed. Pembrolizumab or placebo must be administered as a 30-minute IV infusion Q3W. Sites must make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. Pembrolizumab will be dosed and administered by blinded and qualified study site personnel. The placebo will be a normal saline or dextrose solution prepared by the unblinded pharmacist. The placebo will be dosed and administered by blinded and qualified study site personnel in the same manner as the investigational product (pembrolizumab).

8.1.8.3 FP

Cisplatin 80 mg/m^2 will be administered as a 60 to 120-minute IV infusion or per the site's standard practice on Day 1 of each treatment cycle for up to 6 cycles. Cisplatin may be administered beyond 6 cycles at the discretion of the investigator.

5-FU 800 mg/m^2/day will be administered as a continuous IV infusion from Day 1 to Day 5 (120 hours) of each treatment cycle, after completion of all procedures and assessments according to the Schedule of Assessments.

Investigators are advised to counsel participants assigned to receive 5-FU about risk of photosensitivity and to take sun protection measures accordingly.

8.1.8.4 CAPOX

Oxaliplatin 130 mg/m^2 will be administered as a 2-hour IV infusion or per the site's standard practice on Day 1 of each treatment cycle.

Capecitabine will be administered as a 1000 mg/m^2 dose bid Days 1 to 14 Q3W. The evening dose of capecitabine should be taken approximately 12 hours after the morning dose and should be taken with food, or within 30 minutes after food/meal, with approximately 200 mL of water. Please refer to the product label for additional guidance on administration procedures for capecitabine.

Note: If participant is enrolled later in the day, it is acceptable for only 1 dose taken on Day 1 and bid dosing can resume on Days 2 to 14 and the final dose will be taken in the morning of Day 15.

Investigators are advised to counsel participants assigned to receive capecitabine about the risk of photosensitivity and to take sun protection measures accordingly.

8.1.8.5 Trastuzumab

Trastuzumab will be administered as an IV 8 mg/kg loading dose, and then 6 mg/kg maintenance thereafter Q3W on Day 1 of every treatment cycle.

8.1.8.6 SOX (Japan SOX Cohort Only)

Oxaliplatin 130 mg/m^2 will be administered as a 2-hour IV infusion or per the site's standard practice on Day 1 of each treatment cycle.

S-1 The dose of 40 mg to 60 mg will be administered bid on Days 1 to 14 Q3W. The Day 1 dose of S-1 will be administered after completion of pembrolizumab, trastuzumab, and oxaliplatin infusion. An interval of at least 8 hours should be kept between the evening and morning doses of S-1. The participants should have a meal and take the drug within 60 minutes after the meal. For additional guidance on the treatment method of S-1, see the package insert.

Note: If participant is enrolled later in the day, it is acceptable for only 1 dose to be taken on Day 1. Twice-daily dosing can resume on Days 2 to 14 and the final dose will be taken in the morning of Day 15.

8.1.9 Second Course of Therapy

See Section 6.7 for details concerning Second Course of Therapy.

8.1.10 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 AEs which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

8.1.10.1 Withdrawal From Future Biomedical Research

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

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

8.1.11 Participant Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE PARTICIPANT.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the drug used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study treatment, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or non-study treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

Treatment identification information is to be unblinded ONLY in following situation:

1. For the welfare of the participant, if necessary.
2. Participants requiring Second Course/re-retreatment who completed 35 cycles and stop trial treatment with SD or better and had to discontinue for reason other than disease progression or intolerability or stop trial treatment due to CR (per protocol requirement). Such participant must have experienced radiographic disease progression while off study treatment according to the criteria in Section 6.7.

Every effort should be made to avoid unblinding the participant unless necessary. In the event that unblinding has occurred, the circumstances around the unblinding (eg, date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Every effort should be made to not unblind the Sponsor. Only the principal investigator or delegate and the respective participant's code should be unblinded. Note: PD-L1 status will remain blinded to the participant and the investigator.

8.1.12 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the BICR can be found in the Site Imaging Manual. Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. In general, imaging should include the chest, abdomen, and pelvis.

Note: For the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

Participant eligibility will be determined using local assessment (investigator assessment) based on RECIST 1.1. All scheduled images for all study participants from the sites will be

submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be submitted to the central imaging vendor.

When the investigator identifies radiographic progression per RECIST 1.1, the image must be submitted to the central imaging vendor to perform expedited verification of radiologic PD, and communicate the results to the trial site and Sponsor (see Section 8.2.1.5 and Figure 3). Treatment should continue until PD has been verified by BICR (if initial site-assessed PD was not verified by BICR, each subsequent scan must be submitted to central imaging vendor with verification of PD request until PD has been verified). Regardless of whether PD is verified, if the investigator considers the participant has progressed, but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of randomization. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the central imaging vendor.

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

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 1 year, participants who remain on treatment will have imaging performed every 6 weeks. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator and verified by BICR (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor for BICR.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4

weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the BICR.

Per iRECIST (Section 8.2.1.6), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants with unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 8.2.1.6. 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 with confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 8.2.1.6.

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

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

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (see Section 8.2.1.2) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. All Second Course imaging should be submitted to the central imaging vendor for quality control, storage, and possible retrospective review.

The first on-study imaging assessment should be performed at 6 weeks (42 days +7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently, if clinically indicated.

Per iRECIST (Section 8.2.1.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. In clinically stable participants, disease progression may be confirmed by the investigator using iRECIST 4 to 8 weeks after the first tumor imaging indicating PD.

For participants who discontinue Second Course study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue Second Course study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (42 days ±7 days) until either the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR 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, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. Initial tumor imaging showing site-assessed PD should be submitted immediately for BICR verification of PD. The site will be notified if the BICR verifies PD using RECIST 1.1. Figure 3 illustrates the imaging flow involving verification of PD for clinically stable participants.

8.2.1.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 9. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent to the central imaging vendor for potential retrospective BICR.

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

If a participant has confirmed radiographic progression (iCPD), study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the BICR.

A description of the adaptations and iRECIST process are found in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 15 and illustrated as a flowchart in Figure 3.

Table 15 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.	Submit the imaging to BICR for verification. Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the assessment of the investigator and after the participant's consent	Submit the imaging to BICR for verification. Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
First radiologic evidence of PD by RECIST 1.1 that has been verified by BICR	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete 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; VOP=verification of progression.

Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur. If RECIST 1.1 disease progression has not been centrally verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with VOP request until RECIST 1.1 progression is verified by BICR.

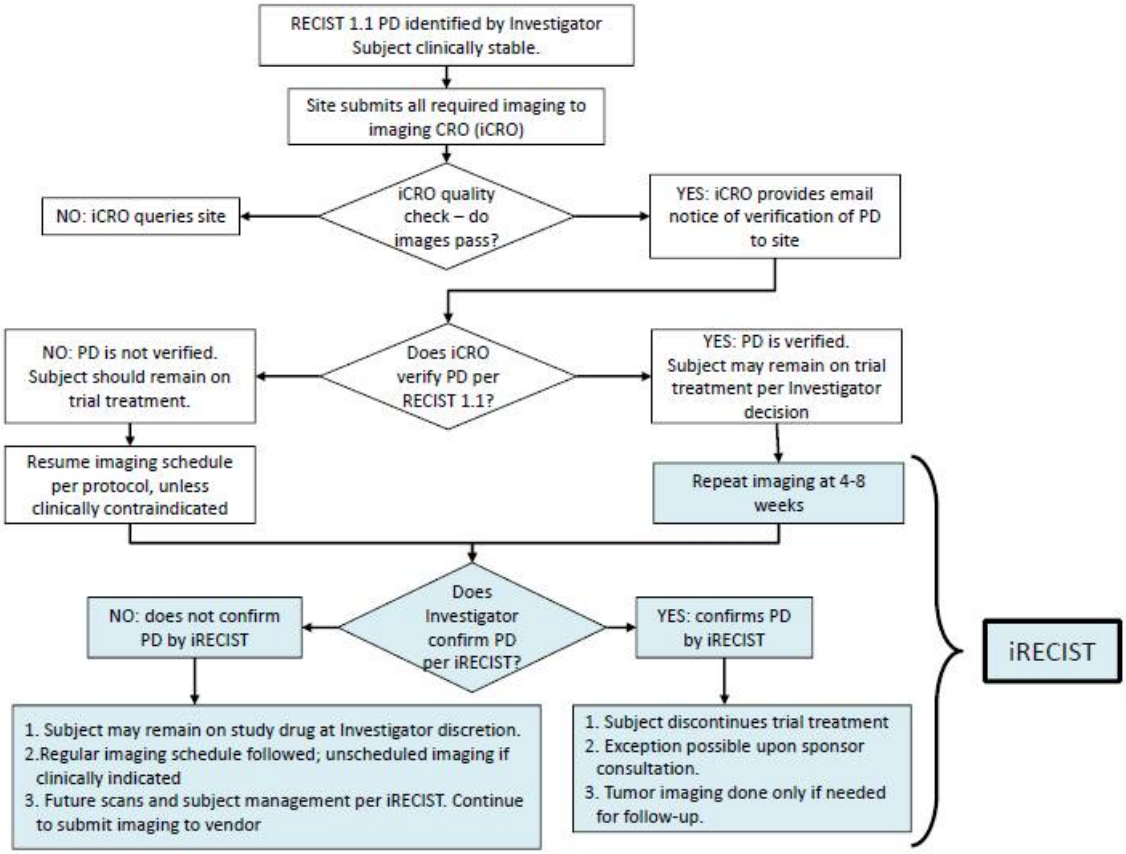


Figure 3 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator

8.2.2 Quality of Life Assessments

8.2.2.1 Patient-Reported Outcomes

The EuroQoL EQ-5D, EORTC QLQ-STO22 and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EuroQoL EQ-5D first, then EORTC QLQ-C30 and EORTC QLQ-STO22. All electronic patient reported outcomes (ePROs) are to be performed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, and Cycle 5 and every 2 cycles thereafter (eg, Cycle 7, Cycle 9, Cycle 11) up to a year or End of Treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit. A visit window of ± 7 days will apply to PRO visit assessments.

It is best practice and strongly recommended that ePROs are administered to randomized participants prior to drug administration, adverse event evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the

MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Exam

For cycles that do not required a full physical exam as defined in Section 1.3, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs.

8.3.1.3 Ophthalmologic Complications due to Capecitabine

Participants should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated as clinically appropriate.

8.3.1.4 Severe Skin Reactions due to Capecitabine

Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. Capecitabine should be permanently discontinued in participants who experience a severe skin reaction during treatment.

8.3.2 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured only at screening. The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study treatment, and at time of study discontinuation as specified in the SoA (Section 1.3).

8.3.3 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed and reviewed by an investigator or medically qualified designee (consistent with local requirements) once at

screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

Note: A 6-lead ECG is allowed per institutional standard

France only: For participants receiving oxaliplatin:

- A 12-lead ECG must be performed on the day of administration before and after intravenous administration of oxaliplatin.

8.3.4 Echocardiography or Multigated Acquisition Scan

An echocardiography (ECHO) or multigated acquisition (MUGA) scan will be required at screening to determine study eligibility. The assessment method will be at the investigator's discretion and per the local standard of care. Additional assessments should be performed according to Section 1.3 and may be performed as clinically necessary.

8.3.5 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 or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 5, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study 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.

8.3.5.1 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of the first dose of study treatment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a

positive test result. Repeated pregnancy testing should be conducted Q3W according to Section 1.3, after the last dose of study treatment, and as required by local regulations.

8.3.6 Audiometry

Audiometry testing will be performed at baseline for participants on the FP chemotherapy backbone, and is repeated during the trial as clinically indicated per the treating physician or designee. Pure tone audiometry is an acceptable method to measure. Other ototoxicity tests per local requirement are also acceptable. It is not acceptable to skip audiometry testing at baseline.

8.3.7 Performance Assessments

8.3.7.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 8) at screening, prior to the administration of each dose of study treatment and during the follow-up period as specified in the SoA (Section 1.3).

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

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 4.

Progression of the cancer under study is not considered an AE as described in Section 8.4.5 and Appendix 4.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment 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 randomization through 7 months following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 16.

Table 16 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Time Period			Time Frame to Report Event and Follow-up Information to SPONSOR:
	Consent to Randomization/ Allocation	**Randomization/ Allocation through Protocol-Specified Follow-up Period**	**After the Protocol Specified Follow-up Period**	
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 drug-induced liver injury (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

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, ECIs, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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 (R2) Guidelines for GCP.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1. Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

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

8.4.6 Pregnancy and Exposure During Breastfeeding

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

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

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and serious adverse events are also known as ECIs 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 8.5, 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).

8.5 Treatment of Overdose

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

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

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

Overdose with other study treatments should follow the prescribed information in their relative package inserts.

8.6 Pharmacokinetics

To evaluate the immunogenicity and exposure of pembrolizumab and trastuzumab in this indication, sample collections for analysis of PK and ADA are currently planned as shown in the SoA (Section 1.3.1). Blood samples for PK and ADA collected will be stored. Analysis will be performed only if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued. Sample collection, storage, and shipment instructions for samples will be provided in the operations/laboratory manual.

8.7 Biomarkers

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

- Blood for Genetic Analysis
- Whole Blood Sample for MSI DNA Analysis
- Blood for RNA Analysis
- Blood for Plasma Biomarker Analyses
- Blood for Serum Biomarker Analyses
- Blood for ctDNA
- Archival or Newly Obtained Tissue Collection
- On-treatment biopsy (optional) if provided

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

The sample for genetic analysis will be drawn for MSI or genotyping and for planned exploratory biomarker research. If the IRB/IEC does not approve of the exploratory biomarker analysis, or if there is a local law or regulation prohibiting the same, biomarker sample collection and data analysis will be limited to MSI. Leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent.

8.8 Future Biomedical Research Sample Collection

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

- Leftover DNA
- Leftover RNA
- Leftover plasma from blood for plasma biomarker analyses
- Leftover serum from blood for serum biomarker analyses
- Leftover plasma from blood for ctDNA
- Leftover main study tumor

8.9 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

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

All hospitalization and emergency room visits must be reported in the eCRF from the time of treatment 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.

8.10 Visit Requirements

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

8.10.1 Screening

8.10.1.1 Pre-screening Period

The Pre-screening period may be utilized by participants to determine biomarker eligibility based on HER2 and PD-L1 status using an archival tumor sample. After signing an authorization for release of tumor tissue form, participants will be assigned a screening number. Characterization of HER2 and PD-L1 status will be performed at a pre-screening visit for participants with an available archival tumor biopsy sample. If the participants are HER2 positive, written consent for the main study will need to be obtained.

Participants who do not have an archival tumor biopsy sample available will not enter the pre-screening period as eligibility based on HER2 expression will be determined in the main study screening period.

8.10.1.2 Screening Period

Approximately 28 days prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

8.10.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8. Unless otherwise specified, assessments/procedures are to be performed prior to administration of study treatment. Unless otherwise specified, the window for each visit is ±3 days.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

8.10.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

8.10.3.2 Follow-up

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (±7 days) by imaging until PD to monitor disease status. Every effort should be made to collect information regarding disease status until disease progression, the start of new anti-cancer therapy, withdrawal of consent, pregnancy, or end of study, whichever occurs first. Information regarding post-study anticancer treatment will be collected if new treatment is initiated. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks).

8.10.3.3 Survival Follow-up Assessments

Participant survival follow-up status will be assessed approximately every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first.

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

For participants who discontinue treatment intervention and who will not enter the Follow-up Phase, the first survival follow-up assessment will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).

For participants who completed assessments in the efficacy follow-up phase, the first survival follow-up assessment will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.10.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to: an external DMC review, interim analysis (IA), and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

8.10.5 Post-study

Participants will be required to return to clinic approximately 30 days after the last dose of study treatment for the post-study visit. If the post-study visit occurs less than 30 days after the last dose of study treatment, a subsequent follow-up telephone call should be made at 30 days post the last dose of study treatment to determine if any AEs have occurred since the post-study clinic visit.

9. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the Global Cohort. If, after the study has begun but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, 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 will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report for the study.

Separate analysis plans may be developed for PK/modeling analysis, biomarker analysis, and genetic data analysis. Post hoc exploratory analyses will be clearly identified in the Clinical Study Report.

The Japan-specific SOX cohort will be analyzed separately. The detailed analyses will be specified in sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan are summarized below; the comprehensive plan is provided in Section 9.2 through Section 9.11.

Study Design Overview	This is a Phase III, randomized, double-blind trial comparing pembrolizumab and placebo, both in combination with trastuzumab plus chemotherapy as first-line treatment in participants with HER2 positive advanced gastric or GEJ adenocarcinoma
Treatment Assignment	Participants will be randomized in a 1:1 ratio to the experimental arm and the control arm. Stratification factors are in Section 6.3.1.1.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	1) Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR 2) Overall survival (OS)
Key Secondary Endpoints	1) Objective response (OR) per RECIST 1.1 assessed by BICR
Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses on PFS and OS will be evaluated by comparing the experimental arm to the control arm using a stratified Log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The stratified Miettinen and Nurminen method with sample size weights will be used for analysis of ORR.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen method [Miettinen, Olli and Nurminen, Markku 1985].

[redacted]

9.2 Responsibility for Analyses/In-house Blinding

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

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been

performed, protocol deviations have been identified, and data have been declared final and complete.

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

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoint

Dual Primary

- **Progression-free survival (PFS) per RECIST 1.1 assessed by BICR**

  PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. See Section 9.6.1 for the censoring rules.

- **Overall Survival (OS)**

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

Secondary

- **Objective Response Rate (ORR) per RECIST 1.1 by BICR**

  Objective Response is defined as a CR or PR (note: only CR or PR prior to a curative surgical resection will be used among participants with curative surgical resection).

- **Duration of Response (DOR) per RECIST 1.1 by BICR**

  For participants who demonstrated CR or PR, duration of response (DOR) is defined as the time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first.

Exploratory

- Methods related to exploratory objectives will be described in the sSAP.

9.4.2 Safety Endpoint

Safety measurements are described in Section 4.2.1.2.

9.4.3 PRO Endpoint

The patient-reported outcome (PRO) endpoints, which include EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D-5L as described in Section 3, will be evaluated. Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analysis (PFS, OS, and ORR). All randomized participants, whether or not treatment was administered, will be included in this population. Any participant who receives a randomization number will be considered to have been randomized. Participants will be included in the treatment group to which they are randomized.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study medication for one or more cycles but receives the correct treatment for the remaining cycles will be analyzed according to the participant's randomized treatment group and a narrative will be provided for any events that occur during the cycle for which the participant was incorrectly dosed.

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

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

In this section, for the stratified analyses, small strata may be collapsed. Please see details in the footnotes of Table 19. Response or progression in the Second Course Phase will not count towards the PFS of the primary endpoint in this trial.

9.6.1.1 Progression-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.1.1) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per

RECIST 1.1 by BICR. Death is always considered as a confirmed PD event. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, one primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anti-cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer therapy. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers discontinuation of treatment due to reasons other than complete response or initiation of new anticancer treatment, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 17.

Table 17 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy[#], if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

[#]New anti-cancer therapy: excluding curative surgical resections (the detailed definition in Section 6.5.3).

As imaging will continue, participants who have curative surgical resection during the study (per protocol Section 6.5.3) will be followed for PFS events after surgery until local recurrence, distant metastasis, or death for the primary analysis of PFS. An additional sensitivity analysis will be conducted for PFS in which these participants will be censored at last disease assessment prior to the time of the curative surgical resections.

9.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.1.1) will be applied to both the stratified log-rank test and the stratified Cox model.

Participants without documented death at the time of analysis will be censored at the date of last contact.

9.6.1.3 Objective Response Rate

The stratified Miettinen and Nurminen method will be used for the comparison of the ORR between the 2 treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported [Miettinen, Olli and Nurminen, Markku 1985]. The stratification factors used for randomization (Section 6.3.1.1) will be applied to the analysis.

9.6.1.4 Duration of Response

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a complete response or partial response will be included in this analysis.

For each DOR analysis, a corresponding summary of the reasons responding subjects are censored will also be provided. Responding subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules are summarized in Table 18.

Table 18 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy[#] initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥ 2 consecutive missed disease assessments or after new anticancer therapy if any	Last adequate disease assessment prior to ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. [#]new anti-cancer therapy: excluding curative surgical resections (the detailed definition in Section 6.5.3).		

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

Table 19 summarizes the primary analysis approach for key efficacy endpoints.

Table 19 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoints			
PFS per RECIST 1.1 by BICR	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are provided in Table 17, Censoring Rules for Primary and Sensitivity Analyses of PFS)
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the last known alive date
Key Secondary Endpoint			
ORR per RECIST 1.1 by BICR	Test and Estimation: Stratified M&N method with sample size weights††	ITT	Participants without assessments are considered non-responders and conservatively included in the denominator

PFS = Progression-free survival; OS = Overall survival; ORR = Objective response rate; ITT = Intention to treat.
† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 6.3.1.1) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.
†† Miettinen and Nurminen method

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests and vital signs.

The analysis of safety results will follow a tiered approach as shown in Table 20. The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Safety parameters or AEs of interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol. Based on a review of historic chemotherapy data and data from ongoing pembrolizumab clinical studies in gastric cancer, there are no AEs of interest that warrant inferential testing for comparison between treatment arms in this study.

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons.

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 event because the population enrolled in this study are in critical conditions and usually experience various adverse events of similar types regardless of treatment, events reported less frequent than 10% of participants would obscure the assessment of overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in one of the treatment groups) and SAEs (≥5% of participants in one of the treatment groups) will be considered Tier 2 endpoints. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences. These analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, Olli and Nurminen, Markku 1985].

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates are provided for Tier 3 safety parameters. For continuous measures such as vital signs, summary statistics for baseline and on-treatment will be provided by treatment group in tabular format.

Table 20 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	AEs (≥10% of participants in one of the treatment groups)	X	X
	Grade 3-5 AEs (≥5% of participants in one of the treatment groups)	X	X
	SAEs (5% of participants in one of the treatment groups)	X	X
Tier 3	AEs (<10% of participants in one of the treatment groups)		X
	Discontinuation due to AE		X
	Change from Baseline Results (laboratory test toxicity grade)		X
X = results will be provided.			

9.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed.

Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

An external Data Monitoring Committee (DMC) will serve as the primary reviewer of the results of the interim analysis (analyses) of the study and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the SPONSOR. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited SPONSOR personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented. Additional logistical details will be provided in the DMC Charter.

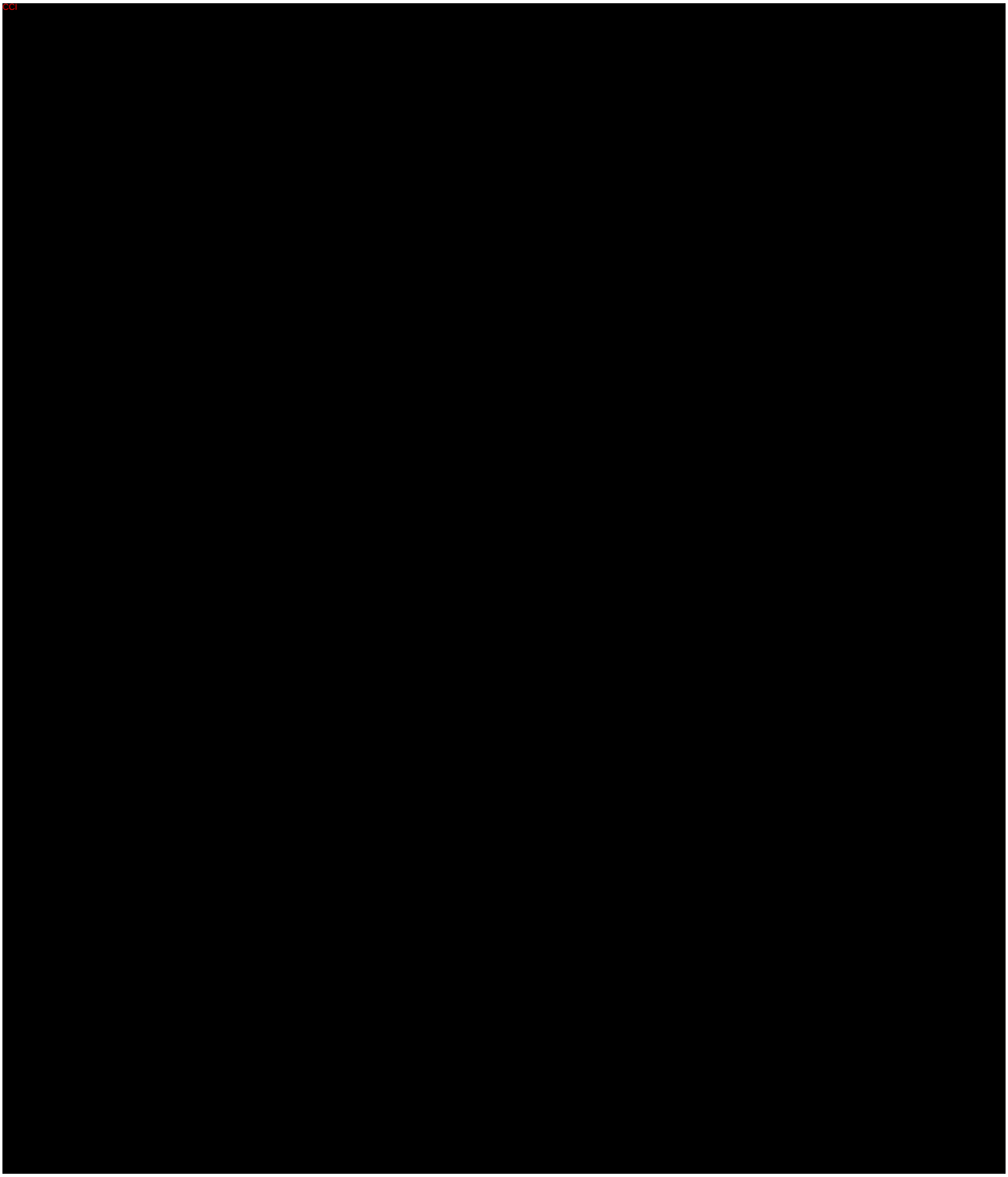
Treatment-level results from the interim analysis will be provided to the DMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

9.7.1 Efficacy Interim Analysis

9.7.2 Safety Interim Analysis

The DMC will be responsible for periodic interim safety reviews as specified in the DMC charter. Interim safety analyses will also be performed at the time of interim efficacy analyses.

9.8 Multiplicity



9.8.2 Progression-free Survival

The initial alpha-level for testing PFS is 0.003. If the null hypothesis for ORR is rejected, Figure 4 shows that half of its alpha, ie, 0.001, is reallocated to PFS hypothesis testing. If the null hypothesis for OS is rejected, then alpha=0.02 is essentially fully reallocated to PFS hypothesis testing. Thus, the PFS null hypothesis may be tested at alpha=0.003, alpha=0.004 (if the ORR null hypothesis is rejected but not the OS null hypothesis), alpha=0.023 (if the OS null hypothesis is rejected but not the ORR null hypothesis), or alpha=0.025 (if both the ORR and OS null hypotheses are rejected). Table 23 shows the boundary properties for each of these alpha-levels for the interim analyses, which were derived using a Lan-DeMets O'Brien-Fleming spending function based on predicted number of events at the planned time of interim analysis. Note that the final row indicates the total power to reject the null hypothesis for PFS at each alpha-level.

If events accrue more slowly than expected or the same as expected, spending will be based on actual information fraction. If events accrue more quickly than expected, cumulative spending based on the expected information fraction will be used in order to save some alpha for analyses that will be performed with more than the originally planned maximum events. For example, at IA2, if 560 PFS events have occurred (ie, more than the expected 542 PFS events), the alpha spending at IA2 will be according to the expected information fraction (542/606=89%) instead of the actual information fraction (560/606=92%).

Also note that if the OS or ORR null hypothesis is rejected at an interim or final analysis, each PFS interim and final analysis test may be compared to its updated bounds considering the alpha reallocation from the OS or ORR hypothesis.

[redacted]

9.8.3 Overall Survival

The OS hypothesis may be tested at alpha=0.02 (initially allocated alpha), alpha=0.023 (if the PFS but not the ORR null hypothesis is rejected), alpha=0.021(if the ORR but not the PFS null hypothesis is rejected), or alpha=0.025 (if both the ORR and PFS null hypotheses are rejected). [redacted]

If events accrue more slowly than expected or the same as expected, spending will be based on actual information fraction. If events accrue more quickly than expected, cumulative spending based on the expected information fraction will be used in order to save some alpha for analyses that will be performed with more than the originally planned maximum events. For example, at IA2, if 420 OS events have occurred (ie, more than the expected 401 OS events), the alpha spending at IA2 will be according to the expected information fraction (401/551 = 73%) instead of the actual information fraction (420/551 = 76%).

Also note that if the PFS or ORR null hypothesis is rejected at an interim or final analysis, each OS interim and final analysis test may be compared to its updated bounds considering the alpha reallocation from the PFS or ORR hypothesis.

9.8.4 Safety Analyses

The external DMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the external DMC can request corresponding efficacy data. External DMC review of efficacy data to assess the overall risk benefit ratio to trial participants will not require a multiplicity adjustment typically associated with a planned efficacy IA; however, to account for any multiplicity concerns raised by the external DMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for efficacy endpoints adopting a conservative multiplicity adjustment will be prespecified in the sSAP. This analysis will be performed if requested by the external DMC.

9.9 Sample Size and Power Calculations

In the Global Cohort, approximately 692 participants will be randomized in a 1:1 ratio between the 2 arms.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of each subgroup. The following are examples of classification variables:

- Age category: (<65 versus ≥65 years)
- Sex: (female, male)
- Race: (Asian versus non-Asian)
- Region: Europe/Israel/North America/Australia versus Asia versus Rest of World (including South America)
- PD-L1: Positive versus Negative
- MSI status
- Primary location: Stomach versus GEJ
- Histological subtype: Diffuse versus intestinal versus indeterminate
- Tumor Burden: ≥ median versus <median
- Number of Metastases: ≤2 versus ≥3
- Prior Gastrectomy: yes versus no

9.11 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in months and number of cycles or administrations as appropriate.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information 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.

10.1.4 Confidentiality of Data

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

10.1.5 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/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.6 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.

Committees Structure

Scientific Advisory Committee

This study was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results and subsequent peer-reviewed scientific publications.

Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC Committee regarding the study.

Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (see Section 9.7 Interim Analyses) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.7 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

10.1.8 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.

10.1.9 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

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

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting

from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

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

10.1.10 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

10.1.11 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.12 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in

the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

13. References

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

10.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

Definitions

Women of Childbearing Potential (WOCBP)

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

Contraception Requirements

Male Participants

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

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

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, and postovulation 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 25 during the protocol-defined time frame in Section 5.1.

Table 25 Highly Effective Contraception Methods

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

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

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

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion

● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 7 months after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. This test should be repeated a maximum of 72 hours before the first dose.

Following initiation of treatment, additional pregnancy testing will be performed Q3W per the SoA (Section 1.3), as clinically indicated during the study, after the last dose of study treatment, and as required locally.

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

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

Definition of AE

AE definition
● An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. ● NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. ● NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use in this study.

Events meeting the AE definition
● Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. ● Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. ● New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. ● Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. ● Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. ● For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 8.4.5 for additional details.

Events NOT meeting the AE definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a preexisting condition that has not worsened. ● Refer to Section 8.4.5 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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the 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, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are 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 AE CRFs/worksheets at each examination. ● It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page. ● There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor. ● The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of intensity

● An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
● The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  ● Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  ● Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
  ● Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  ● Grade 4: Life threatening consequences; urgent intervention indicated.
  ● Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?
  - The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
    - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
      - If yes, did the AE resolve or improve?
        - If yes, this is a positive dechallenge.
      - If no, this is a negative dechallenge.

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

- **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 CRFs/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 AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

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

SAE reporting to the Sponsor via paper CRF

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

10.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 26 will be performed by site's local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 26 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Chemistry	Blood Urea Nitrogen (BUN)[a]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[b]	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Magnesium
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Urine or serum pregnancy test (as needed for WOCBP) • Thyroid function tests (T3/FT3[c], FT4, and TSH) • Coagulation panel (prothrombin time [PT]/ International Normalized Ratio [INR], activated partial thromboplastin time[aPTT])			

a. Urea is acceptable if BUN is not available as per institutional standard.
b. If the test is considered part of standard of care.
c. T3 is preferred; if not available, free T3 may be tested.

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

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.6 Appendix 6: Country-specific Requirements

10.6.1 UK-specific Information:

1. Exclusion Criterion 9: TB testing is mandatory.
2. Exclusion Criterion 19: HIV testing is mandatory.
3. Exclusion Criterion 20: Hepatitis B and C testing is mandatory.
4. Section 6.5.1 Specific Restrictions (Concomitant Therapy) - Live vaccines must not be administered for 90 days after the last study treatment.
5. Section 8.3.5.1 Pregnancy Test; 10.3 Appendix 3 – Pregnancy testing is performed Q3W and after last dose of study treatment per the SoA (Section 1.3).

10.6.2 Germany-specific Information:

1. Exclusion Criterion 9: TB testing is mandatory.
2. Exclusion Criterion 19: HIV testing is mandatory.
3. Exclusion Criterion 20: Hepatitis B and C testing is mandatory.

10.6.3 Japan-specific Information:

1. Approximately 692 participants will be randomized in the Global Cohort. A separate cohort of approximately 40 participants who will receive SOX (S-1 plus oxaliplatin) will be enrolled in Japan for a total of approximately 732 participants. This is in addition to Japan participants enrolled in the Global Cohort. These 40 participants will have their data analyzed separately from the Global Cohort.
2. In Japan, document agreement is necessary for both the participant and their substitute when participants are under 20 years of age.
3. Recommended dose modifications for SOX, oxaliplatin, and S-1 are found in Section 6.6.4.3.

10.6.4 France-specific Information:

For participants receiving oxaliplatin:

- A 12-lead ECG must be performed on the day of administration before and after intravenous administration of oxaliplatin.

10.7 Appendix 7: Abbreviations

Abbreviation/Term	Definition
1L	first line
3L	third line
5-FU	5-fluorouracil
ACC	American College of Cardiology
ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
ADL	activities of daily living
AE	adverse event
AHA	American Heart Association
ALT	alanine aminotransferase
APaT	all participants as treated (population)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BICR	blinded independent central review
BID	2 times a day
BSA	body surface area
C1D1	Cycle 1 Day 1
CAPOX	capecitabine / oxaliplatin
CBC	complete blood count
CD	cluster of differentiation
CHDP	5-chloro-2,4-dihydroxypyridine
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
CPS	combined positive score
CR	complete response
CrCl	calculated creatinine clearance
CRF	case report form

Abbreviation/Term	Definition
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
EG	esophagogastric
EMA	European Medicines Agency
EOC	executive oversight committee
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire-C30
EORTC QLQ-STO22	EORTC Quality of Life Questionnaire-STO22
ePRO	electronic patient-reported outcome(s)
ESMO	European Society for Medical Oncology
EU	European Union
EuroQoL EQ-5D-5L	EuroQoL-5 Dimension Questionnaire
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation/Term	Definition
FISH	fluorescent in-situ hybridization
FP	cisplatin plus 5-fluorouracil
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GEJ	gastroesophageal junction
GI	gastrointestinal
G-SOX	S-1 plus cisplatin versus S-1 plus oxaliplatin study
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
iCPD	iRECIST confirmed progressive disease
IEC	independent ethics committee
iCR	iRECIST confirmed response
Ig	immunoglobulin
IHC	immunohistochemistry
IL-10	interleukin 10
IMP	investigational medicinal product
INR	international normalized ratio
iPD	iRECIST progressive disease
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	modified Response Evaluation Criteria in Solid Tumors for

Abbreviation/Term	Definition
	immune-based therapeutics
IRT	interactive response technology
iSD	iRECIST stable disease
ISH	In situ hybridization
ITT	intention to treat
iUPD	iRECIST unconfirmed progressive disease
IV	intravenous
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI	microsatellite instability
MUGA	multiple-gated acquisition
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
NK	natural killer
NR	not reached
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
Oxo	potassium oxonate
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1

Abbreviation/Term	Definition
PD-L2	programmed cell death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome(s)
PT	prothrombin time
Q3W	every 3 weeks
QLQ	Quality of Life Questionnaire
QoL	quality of life
REAL-2	Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
S-1	combination product containing tegafur , a prodrug of 5-FU, and 2 types of enzyme inhibitors, CDHP and Oxo
SAC	scientific advisory committee
SAE	serious adverse event
SLAB	supplemental lab tests (CRF)
SNP	single nucleotide polymorphism
SoA	Schedule of Activities
SOP	standard operating procedure
SOX	S-1 plus oxaliplatin
SPIRITS	The S-1 plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer study
sSAP	supplemental Statistical Analysis Plan
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
TB	tuberculosis
ToGA	Trastuzumab for Gastric Cancer study

Abbreviation/Term	Definition
TSH	thyroid-stimulating hormone
UA	urinalysis
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBC	white blood cells
WOCBP	woman of child-bearing potential

10.8 Appendix 8: Eastern Cooperative Oncology Group Scale

ECOG Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[ECOG-ACRIN Cancer Research Group 2016]

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

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study treatment until repeat imaging 4 to 8 weeks later is obtained (using iRECIST for participant management). The 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 central verification of site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

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

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

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

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

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new

lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, or if RECIST 1.1 PD has not been verified centrally, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the BICR.

Detection of Progression at Visits after Pseudo-progression Resolves

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

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

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

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

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

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

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