Merck & Co., Inc. policy on posting of redacted study protocols on journal websites is described in Guidelines for Publication of Clinical Trials in the Scientific Literature on the www.merck.com website.

For publicly posted protocols, the Company redacts content that contains proprietary and private information.

This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

Title Page

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

Protocol Title: A Phase 3, randomized, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-859)

Protocol Number: 859-03

Compound Number: MK-3475

Sponsor Name:

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

Legal Registered Address:

One Merck Drive

P.O. Box 100

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

Regulatory Agency Identifying Number(s):

EudraCT	2018-001757-27
IND	123,482

Approval Date: 11 January 2021

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	11-JAN-2021	Amended Statistical Analysis Plan to take into account recently published data, specifically the CM649 and ATTRACTION 4-studies.
Amendment 2	12-DEC-2019	Update Statistical Analysis Plan of the study and provide clarification to specific sections of the protocol.
Amendment 1	20-NOV-2018	Clarify Inclusion/Exclusion Criteria and update Country-specific requirements
Original Protocol	12-JUL-2018	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

[redacted]

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
1.1 Synopsis 4.4 Beginning and End of Study Definition 5.1 Inclusion Criteria 8.1.1 Informed Consent/Assent 8.1.1.1 General Informed Consent 8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research 8.1.3 Participant Identification Card	Updated language in sections to reflect current conditions related to COVID-19 and the ability to obtain written informed consent.	Response to operational changes needed to accommodate COVID-19 conditions and their impact on the informed consent process.

Section # and Name	Description of Change	Brief Rationale
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 8.13.1.2 Screening Period 10.1.8 Data Quality Assurance		
4.2.1.5 Future Biomedical Research 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Removed references to “substudy”	Substudy is not performed in this protocol.
4.1 Overall Design	Added language pertaining to the possibility of the study remaining open for enrollment of additional participants in China	To meet regulatory requirements.
5.1 Inclusion Criteria	Inclusion Criteria #5 and #6 Updated contraception language to most recent iteration	Clarification of information.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion Criterion #21 removed not related to France requirement	No longer required.
5.2 Exclusion Criteria 6.5 Concomitant Therapy	Exclusion Criterion #9 and Section 6.5: Revised language related to vaccines and updated other language for clarity	Clarification of information.
6.4 Study Intervention Compliance	Updated language related to interruptions in study interventions	Clarification of information.
6.5.1.1 Supportive Care Guidelines for Pembrolizumab	Removed/revised language.	Clarification of information.
6.6.1 Initial Treatment or First Course	Inserted Section and moved language from Section 7.1	Clarification of information.
6.6.2 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)	Renamed Section from Dose Modification and Toxicity Management	Clarification of information.
8.1.4 Medical History	Changed wording from “significant” to “important”	Clarification of information.
8.1.8 Study Intervention	Revised language to clarify study intervention administration	Clarification of information.

Section # and Name	Description of Change	Brief Rationale
8.2.1 Tumor Imaging and Assessment of Disease 8.2.1.1 Initial Tumor Scans 8.2.1.2 Tumor Scans During the Study 8.2.1.3 End-of-Treatment and Follow-up Tumor Scans 8.2.1.4 Second Course (Retreatment) Scans	Adjusted language to reflect "scans" instead of "imaging" and other language	Clarification of information.
8.3.5 Pregnancy Test 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 8.4.5 Pregnancy and Exposure During Breastfeeding	Updated and expanded language related to pregnancy testing and outcomes of pregnancy on study in Table 15	Clarification of information.
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs	Revised language.	Clarification of information.

Section # and Name	Description of Change	Brief Rationale
8.10 Planned Genetic Analysis Sample Collection	Revised language.	Clarification of information.
8.13.1.1 Prescreening Period	The word “allowed” was replaced with “preferred” in the sentence: “An archival tissue sample taken up to 1 year prior to study randomization is allowed”	Clarification of information.
8.13.3.2 Efficacy Follow-up Visits 8.13.3.3 Survival Follow-up Assessments 8.13.4 Vital Status	Updated language and titles to clarify visit information	Clarification of information.
[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
10.2 Clinical Laboratory Tests	Changed wording from “abnormal” to “clinically significant” in Table 27	Clarification of information.
10.7.1 Germany-specific Information	Added a country-specific note. Sites in Germany will perform a systematic search for DPD deficiency for participants who have been naive to 5-fluorouracil or capecitabine. This research should be performed before any administration of 5-fluorouracil or capecitabine.	Per the request of a Germany site’s Ethics Committee.
10.7.4 France-specific Information	Added a Country-specific note: Sites in France will perform a systematic search for DPD deficiency for participants who have been naive to 5-fluorouracil or capecitabine. This research should be performed before any administration of 5-fluorouracil or capecitabine.	This country-specific note was moved from Exclusion Criteria #21 to ensure all country-specific information for may be found in the same section.

Section # and Name	Description of Change	Brief Rationale
10.7.5 Italy-specific Information	Added country-specific notes. 1. Participants with significant cardiovascular impairment, including myocardial infarction, within 6 months of the first dose of study intervention should be excluded. 2. Due to clinically significant interaction between brivudine and fluoropyrimidines, recent or concomitant treatment with brivudine (or the analog sorivudine) is contraindicated. Participants on such treatment or with less than 4 weeks since last dose of brivudine (or sorivudine) should be excluded from enrollment. 3. Sites Italy will perform a systematic search for DPD deficiency for participants who have been naive to 5-fluorouracil or capecitabine. This research should be performed before any administration of 5-fluorouracil or capecitabine.	Country-specific requests added to protocol per the request of Italy Health Authority.

Section # and Name	Description of Change	Brief Rationale
10.7.6 Czech Republic-specific Information	Added country-specific information. 1. Exclusion Criterion 18: HIV testing is mandatory. 2. Exclusion Criterion 19: Hepatitis B and C testing is mandatory. 3. Prohibited Concomitant Medications: Live vaccines are prohibited through 3 months after the end of study intervention. 4. Section 6.7 Second Course Phase: Eligibility for retreatment (termed Second Course Phase) is at the medical discretion of the site Principal Investigator provided the study remains open and the participant meets the conditions listed in Section 6.7.	Country-specific requests added to protocol per the request of Czech Republic Health Authority.
Various typographical and minor corrections were made throughout the document		

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, randomized, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-859)

Short Title: Pembrolizumab/placebo plus chemotherapy as first-line therapy in participants with HER2 negative advanced gastric or GEJ adenocarcinoma

Acronym: KEYNOTE-859

Hypotheses, Objectives, and Endpoints:

In male and female participants at least 18 years of age with human epidermal growth factor receptor 2 (HER2) negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma:

Primary Objectives	Primary Endpoints
- Objective: To compare the overall survival (OS) of the participants following administration of pembrolizumab versus placebo when each is combined with chemotherapy - Hypothesis (H1): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in participants with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥10 - Hypothesis (H2): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in participants with PD-L1 positive tumors defined by CPS ≥1 - Hypothesis (H3): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in all participants	- OS: The time from randomization to death due to any cause
Secondary Objectives	Secondary Endpoints
- Objective: To compare the progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), as assessed by blinded independent central review (BICR), following administration of pembrolizumab versus placebo when each is combined with chemotherapy	- PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

- Hypothesis (H4): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in participants with PD-L1 positive tumors defined by CPS ≥10 - Hypothesis (H5): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in participants with PD-L1 positive tumors defined by CPS ≥1 - Hypothesis (H6): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in all participants	
- Objective: To compare the objective response rate (ORR) per RECIST 1.1, as assessed by BICR, following administration of pembrolizumab versus placebo when each is combined with chemotherapy - Hypothesis (H7): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in participants with PD-L1 positive tumors defined by CPS ≥10 - Hypothesis (H8): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in participants with PD-L1 positive tumors defined by CPS ≥1 - Hypothesis (H9): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in all participants	- Objective response (OR): Complete response (CR) or partial response (PR)
- Objective: To describe the duration of response (DOR) per RECIST 1.1, as assessed by BICR, following administration of pembrolizumab versus placebo when each is combined with chemotherapy in participants with PD-L1 CPS ≥10, PD-L1 CPS ≥1, and in all participants	- DOR: The time from first response (CR or PR) to subsequent disease progression, or death from any cause, whichever occurs first
- Objective: To evaluate the safety and tolerability of pembrolizumab plus chemotherapy versus placebo plus chemotherapy	- Adverse events (AEs) - Study intervention discontinuation due to AEs

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment of advanced gastric or GEJ adenocarcinoma
Population	Participants with previously untreated, HER2 negative, advanced gastric or GEJ adenocarcinoma
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Investigator, Participant
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 1542 participants will be randomized. After enrollment of the Global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants from China have been enrolled to meet local regulatory requirements.

Intervention Groups and Duration:

Intervention Groups

Group Name	Intervention Name	Dose Strength	Dose Frequency	Route of Admin.	Use
Pembrolizumab	Pembrolizumab (MK-3475)	200 mg on Day 1 of each cycle	Q3W	IV	Experimental
Placebo	Placebo	Day 1 of each cycle	Q3W	IV	Placebo
Backbone chemotherapy					
FP	Cisplatin	80 mg/m^2 on Day 1 of each cycle	Q3W*	IV	Comparator regimen and combination agent
	5-FU	800 mg/m^2/day continuous on Days 1 to 5 of each cycle (120 hours, or per local standard)	Q3W	IV	Comparator regimen and combination agent
CAPOX	Oxaliplatin	130 mg/m^2 on Day 1 of each cycle	Q3W*	IV	Comparator regimen and combination agent
	Capecitabine	1000 mg/m^2 twice daily on Days 1 to 14 of each cycle	Q3W	Oral	Comparator regimen and combination agent

5-FU=5-fluorouracil; CAPOX=capecitabine and oxaliplatin; FP=cisplatin and 5-fluorouracil; IV=intravenous; Q3W=every 3 weeks
* Duration of cisplatin or oxaliplatin treatment may be capped at 6 cycles as per local country guidelines; however, treatment with 5-FU/capecitabine may continue per protocol.
Investigator decision regarding the type of backbone chemotherapy (FP or CAPOX) should be determined prior to randomization.
Participants should continue on the type of backbone chemotherapy chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor.
Participants who are randomized to placebo are not allowed to crossover to pembrolizumab treatment.

Total Number

2 intervention groups

Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for study discontinuation is met. Participants who complete study intervention after receiving 35 administrations of pembrolizumab, and participants who attain a complete response (CR) and stop study intervention may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) on experiencing disease progression. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until any of the conditions for discontinuation are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study. Once the participant has achieved the study objective or the 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 Committees:

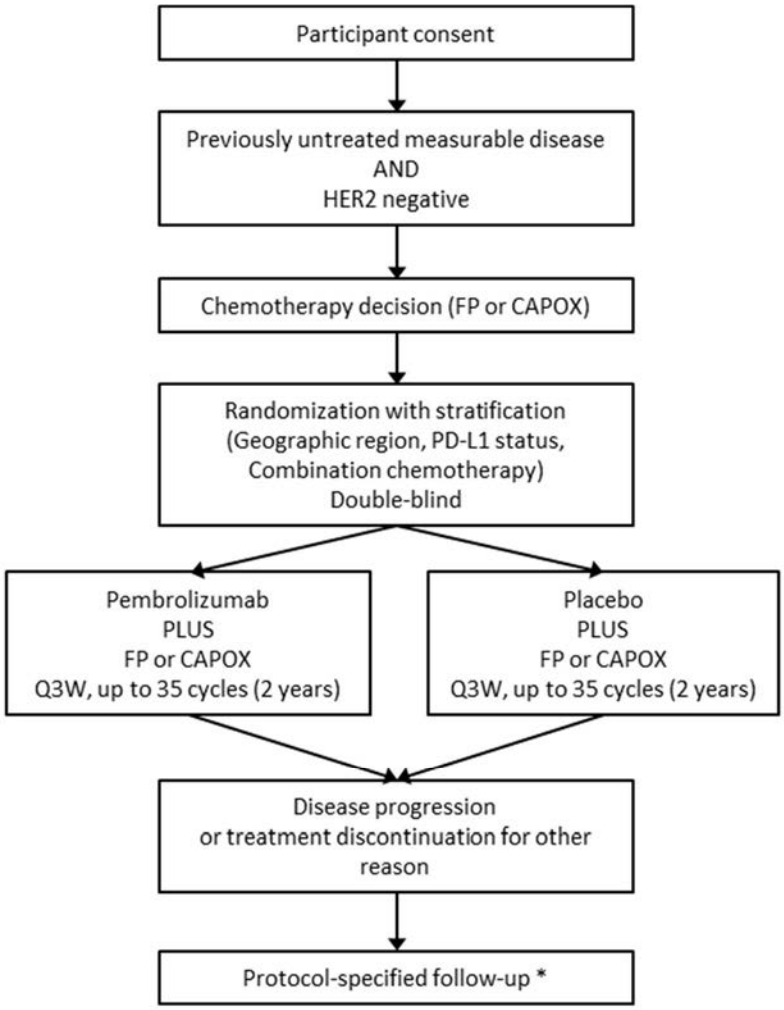
Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.



* Safety follow-up, follow-up , and survival follow-up per protocol procedures.
CAPOX=capecitabine and oxaliplatin; FP=cisplatin and 5-fluorouracil; HER2=human epidermal growth factor receptor 2; Q3W=every 3 weeks

Figure 1 KEYNOTE-859 Study Design

1.3 Schedule of Activities (SoA)

1.3.1 Initial Treatment Phase

Procedures and activities during the Treatment Phase are outlined in Table 1.

Table 1 Study Schedule of Activities – Initial Treatment Phase

Study Period:	Screen-ing Phase	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle		1	2	3	4	5	6 to 35	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing	-28 to -1							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window:		+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
Administrative Procedures												
Informed Consent	X											See footnote "a." Refer to Section 8.1.1.
Reconsent at the First Indication of Radiographic Progression		←——————————→										As assessed by the investigator.
Informed Consent for Future Biomedical Research	X											Not required for participation in the study.
Eligibility Criteria	X											
Participant Identification Card	X											Refer to Section 8.1.3.
Medical History and Demographics	X											Refer to Section 8.1.4.

Study Period:	Screen-ing Phase	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle		1	2	3	4	5	6 to 35	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing	-28 to -1							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window:		+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X			Refer to Section 8.1.5. Prior medications: record all medications taken within 28 days before first dose. Concomitant medications: Enter new medications started during the study through the posttreatment Safety Follow-up. Record concomitant medications beyond 30 days after treatment discontinuation if related to SAE or ECI.
Study Intervention												
Intervention Randomization		X										Site personnel will access IRT after confirming the participant is eligible for randomization.
Pembrolizumab or Placebo Administration		X	X	X	X	X	X					Refer to Section 6.1 for administration instructions. Administration to start on Day 1 of each cycle, after all procedures/ assessments have been completed. Sites should follow local practice guidelines and refer to the appropriate appendix, where indicated.
FP or CAPOX Administration		X	X	X	X	X	X					

Study Period:	Screen-ing Phase	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle		1	2	3	4	5	6 to 35	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing	-28 to -1							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window:		+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
Efficacy Procedures												
Tumor Imaging	X			X		X	X	X		X		Refer to Section 8.2.1. Baseline tumor imaging within 28 days prior to randomization. First on-study imaging at 6 weeks (+ 7 days) after randomization, then every 6 weeks (± 7 days) (or more frequently if clinically indicated).
ePROs (EuroQol EQ-5D, EORTC QLQ-C30, EORTC QLQ-STO22)		X	X	X	X	X	X (odd cycles)	X	X			Refer to Section 8.2.2. It is strongly recommended that ePROs are completed prior to procedures/ assessments, and in the following order: EQ-5D then EORTC QLQ-C30 then EORTC QLQ-STO22. Repeat every 2 cycles after Cycle 5 (eg, Cycle 7, Cycle 9). A visit window of ± 7 days will apply to PRO visit assessments.
Safety Procedures												
Height	X											
Weight	X	X	X	X	X	X	X	X				
Full Physical Examination	X							X				Refer to Section 8.3.1.1

Study Period:	Screen-ing Phase	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle		1	2	3	4	5	6 to 35	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing	-28 to -1							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window:		+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
Directed Physical Examination		X	X	X	X	X	X					Refer to Section 8.3.1.2. Include additional monitoring, as necessary, for participants receiving capecitabine.
Audiometry	X											Only in participants receiving cisplatin. Repeat during the study as clinically indicated.
Vital Signs	X	X	X	X	X	X	X	X				Refer to Section 8.3.2. Include temperature, pulse rate, respiratory rate, and blood pressure.
12-lead ECG (local)	X											Refer to Section 8.3.3.
ECOG Performance Status	X	X	X	X	X	X	X	X				Refer to Section 8.3.5. ECOG performance status for screening is to be performed within 3 days prior to the first dose of study intervention.
AE/SAE Review	X	X	←							→	X	Refer to Section 8.4.
Poststudy Anticancer Therapy Status										X	X	

Study Period:	Screen-ing Phase	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle		1	2	3	4	5	6 to 35	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing	-28 to -1							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window:		+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
Survival Status		←								→	X	Refer to Section 8.13.4. Survival status follow-up starts after investigator-determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study
Laboratory Procedures (LOCAL laboratory)												
Pregnancy Test – Serum or Urine (WOCBP only)	X	X	X	X	X	X	X	X	X			Refer to Appendix 5. During Intervention Phase: test within 72 hours prior to first dose and repeat prior to each treatment cycle and as required by local guidelines.

Study Period:	Screen-ing Phase	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle		1	2	3	4	5	6 to 35	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing	-28 to -1							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window:		+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
HIV, Hepatitis B and C Screen (per local regulations)	X											
PT/INR and aPTT	X											PT/INR should be tested at Screening (within 10 days prior to the first dose of study intervention). Repeat as needed for participants on warfarin-based anticoagulation therapy.
Hematology (CBC with Differential)	X		X	X	X	X	X	X	X			Refer to Section 8.3.4. Laboratory tests for screening are to be performed within 10 days prior to the first dose of study intervention. Then up to 72 hours prior to the scheduled time point.
Chemistry Panel	X		X	X	X	X	X	X	X			
T3 (or Free T3), Free T4, and TSH	X		X		X		X (even cycles)		X			Thyroid function tests should be performed at Screening, then on Day 1 of every other cycle starting from Cycle 2.
Urinalysis	X											Refer to Section 8.3.4.1.

Study Period:	Screen-ing Phase	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle		1	2	3	4	5	6 to 35	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing	-28 to -1							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window:		+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
Laboratory Procedures (CENTRAL laboratory)												
Whole Blood Sample for MSI DNA Analysis[b]		X										Use an EDTA tube. If sample is not available at Cycle 1, it must be collected at a subsequent cycle..
Blood for Genetic Analyses[c]		X										See footnote "c."
Blood for ctDNA Analyses[d]		X	X	X		X	X	X				Collect predose. See footnote "d". ~~This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.~~
Blood for RNA Analyses		X	X			X		X				
Blood for Plasma Biomarker Analysis		X	X			X		X				
Blood for Serum Biomarker Analysis		X	X			X		X				
Tumor Tissue Collection												
Archival or Newly Obtained Tissue Collection[e]	X							X (optional if recurrence)				See Footnote "e." PD-L1 expression status must be known prior to randomization.

Study Period:	Screen-ing Phase	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle		1	2	3	4	5	6 to 35	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing	-28 to -1							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window:		+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	

AE=adverse event; aPTT=activated partial thromboplastin time; CAPOX=capecitabine and oxaliplatin; CBC=complete blood count; ctDNA=circulating tumor deoxyribonucleic acid; d/c=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EDTA=ethylenediaminetetraacetic acid; ePRO=electronic patient-reported outcome(s); FBR=future biomedical research; FP=cisplatin and 5-fluorouracil; HER2=human epidermal growth factor receptor 2; HIV=human immunodeficiency virus; INR=international normalized ratio; IEC=Independent Ethics Committee; IRB=Institutional Review Board; IRT=interactive response technology; MSI=microsatellite instability; PCR= polymerase chain reaction; PD=progressive disease; PD-L1=programmed cell death ligand 1; RNA=ribonucleic acid; PT=prothrombin time; SAE=serious adverse event; SOP=standard operating procedure; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=woman/women of childbearing potential

a. 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 (ie, within 28 days prior to the first dose of study intervention). The form for authorization for release of tumor tissue may be signed prior to the screening period 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, blood and tumor tissue is required. A blood sample 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. Blood for genetic analyses: This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

d. Following C3D1 collection, the ctDNA samples should be collected at the subsequent imaging, and then every 6 weeks (± 7 days) following the imaging schedule until the end of treatment.

e Archival or newly obtained tissue collection: Baseline tumor tissue for biomarker analysis from a newly obtained core or excisional biopsy (fine needle aspirate not adequate) or prior archival tissue specimen must be provided. 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. It is preferred to have an archival tumor tissue sample taken up to 1 year prior to study randomization, however samples more than 1 year old are acceptable. In the absence of more updated histology to confirm metastatic gastric/GEJ adenocarcinoma, we do ask the PI to confirm their clinical opinion that any recurrence represents recurrence of the original gastric/GEJ adenocarcinoma, and not some other new primary malignancy. If the participant signs the FBR consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR. Optional biopsy may be collected at recurrence if the participant consents.

1.3.2 Second Course (Retreatment) Phase

This phase is open only to participants who were originally randomized to receive pembrolizumab plus chemotherapy, and who meet the eligibility criteria for retreatment specified in Section 6.7. Procedures and activities are outlined in Table 2.

Table 2 Study Schedule of Activities – Second Course (Retreatment) Phase

Study Period:	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle	1	2	3	4	5	6 to 17	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted.
Scheduled Timing							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	Posttreatment Period: Refer to Section 8.13.3.
Window	+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			Refer to Section 8.1.5.2. Concomitant medications: Enter new medications started during the study through the posttreatment Safety Follow-up. Record concomitant medications beyond 30 days after treatment discontinuation if related to SAE or ECI.

Study Period:	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle	1	2	3	4	5	6 to 17	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted.
Scheduled Timing							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	Posttreatment Period: Refer to Section 8.13.3.
Window	+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
Study Intervention											
Pembrolizumab	X	X	X	X	X	X					Refer to Section 6.1 for administration instructions. To be administered on Day 1 of each cycle after all procedures/ assessments have been completed. The participant may resume the same previously administered systemic cytotoxic chemotherapy at the discretion of the local site investigator.
Efficacy Procedures											
Tumor Imaging	X		X		X		X		X		Refer to Section 8.2.1. Within 28 days prior to restarting pembrolizumab First on-treatment image at 6 weeks (+ 7 days), then every 6 weeks (± 7 days) (or more frequently if clinically indicated)
Safety Procedures											
Weight	X	X	X	X	X	X	X				
Full Physical Examination	X						X				Refer to Section 8.3.1.1.
Directed Physical Examination		X	X	X	X	X					Refer to Section 8.3.1.2.
Vital Signs	X	X	X	X	X	X	X				Refer to Section 8.3.2 Include temperature, pulse rate, respiratory rate, and blood pressure.

Study Period:	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle	1	2	3	4	5	6 to 17	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window	+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
ECOG Performance Status	X	X	X	X	X	X	X				Refer to Section 8.3.5. Within 3 days prior to restarting pembrolizumab.
AE/SAE Review	X	←							→	X	Refer to Section 8.4.
Poststudy Anticancer Therapy Status									X	X	
Survival Status	←								→	X	Refer to Section 8.13.4. Survival follow-up starts after investigator-determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures (LOCAL laboratory)											
Pregnancy Test – Serum or Urine (WOCBP only)	X	X	X	X	X	X	X	X			Refer to Appendix 5. During Intervention Phase: Test within 72 hours prior to restarting pembrolizumab and repeat prior to each treatment cycle, and as required by local guidelines.
PT/INR and aPTT	X										Test within 10 days prior to restarting pembrolizumab. Repeat as needed for participants on warfarin-based anticoagulation therapy.

Study Period:	Intervention Phase (Every 3 Weeks)						End of Treatment	Posttreatment			**Notes**
Treatment Cycle	1	2	3	4	5	6 to 17	Discontin-uation	Safety Follow-up	Efficacy Follow-up	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Posttreatment Period: Refer to Section 8.13.3.
Scheduled Timing							At time of d/c	30 days post last dose	Every 6 weeks post last dose	Every ~12 weeks (telephone)	
Window	+3	± 3	± 3	± 3	± 3	± 3		+ 7	± 7	± 14	
Hematology (CBC with Differential)	X	X	X	X	X	X	X	X			Refer to Section 8.3.4. Within 7 days prior to restarting pembrolizumab. Then up to 72 hours prior to the scheduled time point.
Chemistry Panel	X	X	X	X	X	X	X	X			
T3 (or Free T3), Free T4, and TSH	X	X		X		X (even cycles)		X			Thyroid function tests should be performed at Cycle 1 Day 1 and every other cycle starting from Cycle 2.
Urinalysis	X										Refer to Section 8.3.4 Within 7 days prior to restarting pembrolizumab

AE=adverse event; aPTT=activated partial thromboplastin time; CBC=complete blood count; d/c=discontinuation; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; INR=international normalized ratio; PD=progressive disease; PT=prothrombin time; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential

2 INTRODUCTION

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]. In 2012, there were approximately 952,000 new cases of gastric cancer worldwide (631,000 men and 320,000 women) with 723,000 deaths (469,000 men and 254,000 women), making it the third-leading cause of cancer death globally in both sexes [Ferlay, J., et al 2014]. 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 EU, approximately 82,000 new cases of gastric cancer were diagnosed in 2012, with approximately 58,000 deaths attributed to this disease. Corresponding numbers in the US showed an estimated 21,000 new cases of gastric cancer with nearly 12,000 deaths from this disease.

2.1 Study Rationale

Accumulating evidence demonstrates that combining the PD-1 targeted mAb pembrolizumab with current standard-of-care cytotoxic chemotherapy for the treatment of advanced, unresectable and/or metastatic cancer improves clinical outcomes [Robert, C., et al 2015] [Gandhi, L., et al 2018]. This has been most recently demonstrated by the randomized, double-blind, Phase 3 KEYNOTE-189 study which showed that addition of pembrolizumab to standard cytotoxic chemotherapy in the first-line treatment setting of metastatic non-squamous non-small cell lung carcinoma (NSCLC) (without sensitizing EGFR or ALK mutations) resulted in statistically significant improvements in OS and PFS. KEYNOTE-189 enrolled patients regardless of PD-L1 status. In this PD-L1 “all-comer” population of patients with metastatic non-squamous NSCLC, the addition of pembrolizumab to standard cytotoxic chemotherapy was associated with a 48% reduction in the risk of disease progression and a 51% reduction in the risk of death when compared to chemotherapy plus placebo. The occurrence of Grade 3 or higher toxicities occurred with similar frequency in both the pembrolizumab and placebo arms of the study [Gandhi, L., et al 2018].

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 chemotherapy regimens for patients with metastatic gastric cancer. Though cytotoxic chemotherapy alone is the mainstay of treatment, newer molecularly targeted immunotherapy agents have been added to standard chemotherapy regimens to improve clinical outcomes in advanced, metastatic gastric and GEJ adenocarcinoma.

The anti-PD-1 monoclonal antibody pembrolizumab has demonstrated durable immune-mediated antitumor activity in patients with advanced gastric cancer.

Clinical proof of concept demonstrating activity of pembrolizumab in participants with advanced gastric cancer came from Cohort D of the Phase 1b KEYNOTE-012 study. This cohort enrolled 39 participants with PD-L1 positive advanced gastric or GEJ adenocarcinoma

[Muro, K., et al 2016]. Eight of 39 participants had an OR by RECIST 1.1 using BICR for an ORR of 22% (95% CI: 10, 39).

The antitumor activity of pembrolizumab in locally advanced, unresectable and/or metastatic gastric or GEJ adenocarcinoma was further characterized in the Phase 2 KEYNOTE-059 study which involved 3 separate cohorts of participants.

Cohort 1 tested pembrolizumab monotherapy as third-line and above treatment of advanced gastric/GEJ adenocarcinoma, regardless of PD-L1 expression. In this all-comer population of highly pre-treated participants for whom there were no alternative effective agents, pembrolizumab monotherapy demonstrated durable objective responses with a clinically meaningful ORR of 12%. A higher response rate (16%) was observed in the PD-L1 positive population [Wainberg, Z. A., et al 2017]. Based on data from KEYNOTE-059, pembrolizumab received accelerated approval by the US FDA in September 2017, for treatment of third-line and above patients with tumors expressing PD-L1 (CPS ≥1) assessed by an FDA-approved test.

Cohorts 2 and 3 evaluated pembrolizumab in the first-line treatment setting among participants with advanced, unresectable and/or metastatic gastric and GEJ adenocarcinoma. In both cohorts, ORR was assessed according to RECIST 1.1 by BICR.

Cohort 2 (n=25) enrolled participants regardless of PD-L1 expression; these participants received the combination of pembrolizumab and standard-of-care cytotoxic chemotherapy consisting of cisplatin plus a fluoropyrimidine. This combination yielded an ORR of 60% (95% CI: 39, 79) and a 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% CI: 8.6, NR) [Wainberg, Z. A., et al 2017]. By historical comparison, this OS result compares favorably with that seen in the ML17032 study, which administered cisplatin and 5-FU (treatment regimen known as FP) or cisplatin and capecitabine (treatment regimen known as XP) alone to patients with advanced gastric cancer. Median OS for patients on the ML17032 study who received FP or XP alone was 9.3 months and 10.5 months, respectively [Ryu, M. H. 2009].

Cohort 3 (n=31) enrolled participants with PD-L1 positive [CPS ≥1] gastric/GEJ adenocarcinoma; these participants received pembrolizumab monotherapy which yielded an ORR of 26% (95% CI: 12, 45) and a median OS of 20.7 months (9.2, 20.7) [Wainberg, Z. A., et al 2017].

KEYNOTE-061 was a global Phase 3 study of single-agent pembrolizumab versus single-agent paclitaxel in the second-line treatment setting of advanced gastric and GEJ adenocarcinoma that progressed after first-line therapy with both a platinum and fluoropyrimidine agent. The study initially enrolled participants regardless of PD-L1 status. In the most recent analysis of this study [Fuchs, C. S., et al 2018], 67% of enrolled participants had PD-L1 CPS ≥1. The ORR associated with single-agent pembrolizumab was 15.8% (95% CI: 11.0, 21.7); this compared favorably with the ORR associated with paclitaxel of 13.6% (95% CI: 9.1, 19.1). Median DOR for pembrolizumab and paclitaxel was 18.0 months (1.4, 26.0) and 5.2 months (1.3, 16.8), respectively. Median OS, the primary

endpoint, was 9.1 months with pembrolizumab versus 8.3 months with paclitaxel (HR 0.82, 1-sided p=0.042). In participants with previously treated advanced and/or metastatic gastric and GEJ adenocarcinoma and PD-L1 CPS ≥1, pembrolizumab reduced numerically, but not statistically, the risk of death by 18% versus paclitaxel. The results from KEYNOTE-061, taken together with those from KEYNOTE-059, clearly indicate pembrolizumab is active in gastric cancer.

Pembrolizumab has been granted accelerated approval for 'third-line and above' treatment of patients with recurrent, locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥1), as determined by an FDA-approved test. Patients are required to have evidence of disease progression on or after 2 or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response.

This multicenter study will determine antitumor activity and safety of pembrolizumab in combination with standard treatment (FP or capecitabine and oxaliplatin [treatment regimen known as CAPOX]) as first-line therapy in participants with advanced, unresectable metastatic gastric or GEJ adenocarcinoma. Participants will be eligible regardless of PD-L1 expression status to ensure inclusion of the entire spectrum of first-line gastric cancers. As per internal Merck data, approximately 70% of participants are predicted to have PD-L1 positive tumor expression.

The study is being powered for biomarker-enriched populations PD-L1 CPS ≥10 and MSI-H. The rationale for this change emanates from recently presented data showing clinically meaningful improvements in ORR and favorable trends in PFS and OS among CPS ≥10 patients with the addition of pembrolizumab to standard-of-care cytotoxic chemotherapy in the first-line treatment setting of advanced/metastatic gastric and GEJ adenocarcinoma [Tabernero, J., et al 2019]. Internal unpublished data has shown a remarkable treatment effect for the combination of pembrolizumab and SOC chemotherapy versus chemotherapy alone as first-line treatment of MSI-H advanced/metastatic gastric/GEJ adenocarcinoma.

2.2 Background

PD-1 is a key immune checkpoint receptor that is expressed by activated T cells. Tumors use the PD-1 pathway to evade immune surveillance. The PD-1 receptor, on the surface of activated T cells, binds to its ligands PD-L1 and PD-L2, which are expressed on tumor cells, thereby causing immunosuppression and preventing the immune system from rejecting the tumor.

Pembrolizumab is a potent humanized IgG4 mAb with high specificity to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications. For more details on specific indications, refer to the Investigator's Brochure.

2.2.1 Pharmaceutical and Therapeutic 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 CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ T-regs 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. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an 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 CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in gastric and GEJ adenocarcinoma.

Pembrolizumab has been approved by the US FDA for multiple indications, including treatment of advanced, metastatic melanoma, cervical cancer, primary mediastinal B-cell lymphoma, NSCLC, head and neck squamous cell carcinoma, urothelial carcinoma, gastric cancer as well as relapsed/refractory classical Hodgkin Lymphoma and MSI-H (mismatch repair deficient) malignancies. For more information, refer to the Investigator's Brochure.

2.2.2 Preclinical and Clinical Studies

Preclinical studies in mouse models have shown that administration of antibodies blocking the PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and leads

ultimately to tumor rejection. Murine PD-1 or antimouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and generation of IFNγ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [Ropponen, K. M., et al 1997] [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008] [Pölcher, M., et al 2010] [Okazaki, T., et al 2001] [Greenwald, R. J., et al 2005]. Studies have confirmed the in vivo efficacy of PD-1 blockade as monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (refer to the Investigator's Brochure).

Clinical studies have demonstrated efficacy of pembrolizumab in participants with advanced melanoma, NSCLC, head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma.

2.2.3 Ongoing Clinical Studies of Pembrolizumab in Malignancies

Clinical studies involving pembrolizumab are currently ongoing in participants with a number of advanced solid tumor and hematologic malignancies (Table 3). These studies include, but are not limited to, advanced melanoma, NSCLC, and gastric and GEJ adenocarcinomas.

Table 3 Ongoing Clinical Studies of Pembrolizumab in the Gastric Cancer Indication

Study	Phase	Intervention
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, 2L treatment
KN062	3	Pembrolizumab versus pembrolizumab plus FP, placebo plus FP, 1L treatment in PD-L1 positive participants
KN063	3	Pembrolizumab versus paclitaxel, 2L 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
KN811	3	Pembrolizumab plus trastuzumab plus FP/CAPOX versus placebo plus trastuzumab plus FP/CAPOX; 1L treatment of HER2-positive advanced metastatic gastric/GEJ adenocarcinoma

1L=first-line; 2L=second-line; 3L=third-line; 5-FU=5-fluorouracil; CAPOX=capecitabine and oxaliplatin; FP=cisplatin and 5-fluorouracil; GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; KN=KEYNOTE; PD-L1=programmed cell death ligand 1

For study details, refer to the Investigator's Brochure and clinicaltrials.gov.

2.2.4 Information on Other Study-related Therapy

Despite a large number of randomized studies, there is no globally accepted standard first-line chemotherapy regimen in HER2 negative, advanced, unresectable and/or metastatic gastric and GEJ adenocarcinoma. In general, combination chemotherapy regimens provide higher response rates than do single agents. Many patients are recommended to receive a fluoropyrimidine-platinum doublet over more toxic triplet chemotherapeutic regimens.

The fluoropyrimidine/platinum doublet combination is a common first-line therapy for metastatic gastric cancer and it is considered "preferred" by the NCCN Gastric Cancer Guideline committee [National Comprehensive Cancer Network 2016]. Fluoropyrimidine/platinum doublet regimens containing 5-FU or capecitabine and cisplatin or oxaliplatin are recognized worldwide as standard first-line chemotherapy regimens for patients with metastatic gastric and GEJ adenocarcinoma.

The ML17032 study was a randomized, Phase 3 study that compared the combination of cisplatin and capecitabine (XP) to the combination of cisplatin and 5-FU (FP) as first-line treatment in patients with previously untreated advanced gastric cancer [Ryu, M. H. 2009]. No difference was seen in median PFS and the results of this study suggest that capecitabine is at least as effective as 5-FU in the treatment of patients with advanced gastroesophageal cancers.

The REAL-2 study was a randomized, multicenter, Phase 3 study comparing capecitabine with 5-FU and oxaliplatin with cisplatin in 1002 patients with advanced esophagogastric cancer [Cunningham, D., et al 2008]. Results from this study suggest that capecitabine and oxaliplatin are as effective as 5-FU and cisplatin, respectively, in patients with previously untreated esophagogastric cancer.

A meta-analysis of the REAL-2 and ML17032 studies suggested that OS was superior in the 654 patients treated with capecitabine-based combinations compared with the 664 patients treated with fluorouracil-based combinations, although no statistically significant difference in PFS between the treatment groups was seen [Okines, A. F., et al 2009].

Most commonly used doublet regimens are XP, FP, CAPOX, and 5-FU/oxaliplatin (known as FOLFOX). Choices among these regimens are typically based on patients' general medical condition and comorbidities in consideration of the different toxicity profiles of the regimens. This practice pattern is supported by global consensus guidelines for treatment of advanced gastric cancer which recommend use of any of the doublet regimen discussed above [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. These 2 regimens are expected to have similar efficacy, and these regimens will allow investigators a choice based on each patient's medical condition.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from study intervention 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 described above from multiple studies of pembrolizumab, and chemotherapy in the target population, indicate a strong risk:benefit ratio.

Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying Investigator's Brochure and ICF documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

In male and female participants at least 18 years of age with human epidermal growth factor receptor 2 (HER2) negative, previously untreated, unresectable or metastatic gastric or GEJ adenocarcinoma:

Objectives	Endpoints
Primary	
• Objective: To compare the OS of the participants following administration of pembrolizumab versus placebo when each is combined with chemotherapy - Hypothesis (H1): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in participants with PD-L1 CPS ≥10 - Hypothesis (H2): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in participants with PD-L1 positive tumors defined by CPS ≥1 - Hypothesis (H3): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in all participants	• OS: The time from randomization to death due to any cause

Objectives	Endpoints
Secondary	
• Objective: To compare the PFS per RECIST 1.1, as assessed by BICR, following administration of pembrolizumab versus placebo when each is combined with chemotherapy - Hypothesis (H4): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in participants with PD-L1 positive tumors defined by CPS ≥10 - Hypothesis (H5): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in participants with PD-L1 positive tumors defined by CPS ≥1 • Hypothesis (H6): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in all participants	• PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
• Objective: To compare the ORR per RECIST 1.1, as assessed by BICR, following administration of pembrolizumab versus placebo when each is combined with chemotherapy - Hypothesis (H7): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in participants with PD-L1 positive tumors defined by CPS ≥10 - Hypothesis (H8): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in participants with PD-L1 positive tumors defined by CPS ≥1 - Hypothesis (H9): Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in all participants	• OR: CR or PR
• Objective: To describe the DOR per RECIST 1.1, as assessed by BICR, following administration of pembrolizumab versus placebo when each is combined with chemotherapy in participants with PD-L1 CPS ≥10, PD-L1 CPS ≥1, and in all participants	• DOR: The time from first response (CR or PR) to subsequent disease progression, or death from any cause, whichever occurs first
• Objective: To evaluate the safety and tolerability of pembrolizumab plus chemotherapy versus placebo plus chemotherapy	• AEs • Study intervention discontinuation due to AEs

Objectives	Endpoints
Tertiary/Exploratory	
• Objective: To compare the changes from baseline in health-related quality-of-life assessments, using the EORTC QLQ-C30 and the EORTC QLQ-STO22, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	• EORTC QLQ-C30 scores • EORTC QLQ-STO22 scores
• Objective: To characterize utilities, using the EQ-5D™, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	• EuroQoL EQ-5D-5L scores
• To compare PFS and ORR using modified RECIST 1.1 for iRECIST, as assessed by the investigator, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	• PFS using iRECIST • OR using iRECIST
• 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 and other treatments	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other biomarkers

The study will be considered to have met its primary objective if at least 1 primary hypothesis is statistically significant.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multicenter, double-blinded, efficacy and safety study of pembrolizumab or placebo in combination with chemotherapy (FP or CAPOX) in participants with previously untreated, HER2 negative, advanced gastric or GEJ adenocarcinoma.

Approximately 1542 participants will be randomized. After enrollment of the Global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants from China have been enrolled to meet local regulatory requirements. will be randomized in a 1:1 ratio to receive pembrolizumab or placebo in combination with chemotherapy. Participants will be stratified by geographic region, PDL1 tumor expression status (CPS <1, ≥1), and combination chemotherapy (FP or CAPOX). The study is double-blind with respect to randomized study intervention (pembrolizumab/placebo). The investigator has 2 choices of combination chemotherapy

regimen, FP or CAPOX, which must be chosen prior to randomization in the study. Participants should continue on the type of chemotherapy regimen chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor.

Participation in this study will be dependent upon supplying a tumor tissue specimen. Newly obtained endoscopic biopsy or core biopsy of a metastatic site, if obtained as part of normal clinical practice, is preferred to archived samples. Both formalin solution and FFPE 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. Only participants whose tumors do not express HER2 will be eligible for randomization in this study. The specimen will also be evaluated for PD-L1 expression status, and for other biomarker analyses if local laws or regulations permit.

Study intervention administration will begin on Day 1 of each 3-week dosing cycle. Study interventions should begin on the day of randomization or as close as possible to the date on which the participant is allocated/assigned.

Participants will have baseline imaging performed at screening, and the first on-study imaging will be done at Week 6 (+ 7 days) after randomization. No early window is allowed for the initial scheduled Week 6 visit. Subsequently, imaging will be performed every 6 weeks (± 7 days) after randomization, independent of any treatment delays, to assess response to treatment using RECIST 1.1. Study intervention administration will continue until first evidence of PD, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements, administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations (approximately 2 years) of treatment. Participants who attain an investigator-determined confirmed CR may consider stopping study intervention after receiving at least 8 study intervention administrations in total and at least 2 additional administrations of study intervention (including 2 doses of pembrolizumab or matching placebo and at least 80% of the planned doses of combination chemotherapy) beyond the date when the initial CR was declared. Participants who are randomized to placebo are not allowed to crossover to pembrolizumab treatment.

RECIST 1.1 responses as assessed by BICR will be used for the primary efficacy endpoint of PFS. RECIST 1.1 will be used by the local site for treatment decisions until verification of PD by the iCRO. 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 modified RECIST 1.1 for iRECIST (Section 8.2.1.6, Appendix 8), 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 NCI CTCAE version 4.0.

Participants who stopped study intervention after achieving SD or better may be eligible to receive additional pembrolizumab for up to 17 cycles if they experience radiographic disease progression while off study intervention, 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 intervention, and are able to participate in the Second Course Phase only if they were receiving pembrolizumab originally, and if the study remains open. 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 study. The decision to re-treat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of study intervention and the participant still meets the safety parameters listed in the Inclusion/Exclusion criteria (refer to Section 6.7 for further details). During this phase, the participant may resume the same previously administered systemic cytotoxic chemotherapy at the discretion of the local site investigator.

After the end of treatment, each participant will have a 30-day follow-up safety assessment for AE monitoring (refer to Section 8.4.1 for time periods for reporting of SAEs and pregnancy). Participants who discontinue treatment for reasons other than PD will have posttreatment follow-up imaging for disease status until PD, initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be contacted approximately every 12 weeks, or more often as needed, for OS until death, withdrawal of consent, or the end of the study, whichever comes first.

One interim efficacy analysis is planned in this study. Details about interim analyses are provided in Section 9.7. An independent external DMC will monitor the safety and efficacy of this study.

This study will be conducted in conformance with GCP.

After enrollment of the Global portion of the study is complete, the study may remain open to enrollment in a possible China extension until the target number of participants in China has been enrolled to meet local regulatory requirements. A possible extension portion of the study will be identical to the global study (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, and study procedures). Details pertaining to the statistical analyses for participants enrolled in China will be provided in a separate section of the sSAP.

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoints in this study are OS and PFS.

OS is the gold standard for a "hard endpoint" in clinical studies in the area of oncology. However, OS results, especially in the first-line setting, are often confounded by subsequent therapy. In the United States/European Union, gastric cancer is a rare tumor type and most patients have advanced or metastatic disease at the time of diagnosis. Because of the multiple companies developing this class of drugs for gastric cancer, it is expected that a significant proportion of control group participants will subsequently be treated with alternative immunotherapy outside of this protocol.

In this study, PFS 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 an iCRO 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 verification of radiologic progression, as determined by BICR, will be communicated to the site.

The largest meta-analysis (36 studies, 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 study will use the dual endpoints 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.

Secondary efficacy endpoints include OR and DOR.

OR by RECIST 1.1 criteria, as assessed by BICR, is considered evidence of efficacy and is a secondary endpoint for this study. Substantial improvement of OR that is accompanied by duration of response will be considered a clinically important measure of benefit. The ORR will be calculated as the proportion of participants with OR.

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

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

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 progressive disease (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 Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions .

4.2.1.2 Safety Endpoints

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

4.2.1.3 Patient-reported Outcomes

The EORTC QLQ-C30 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.

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

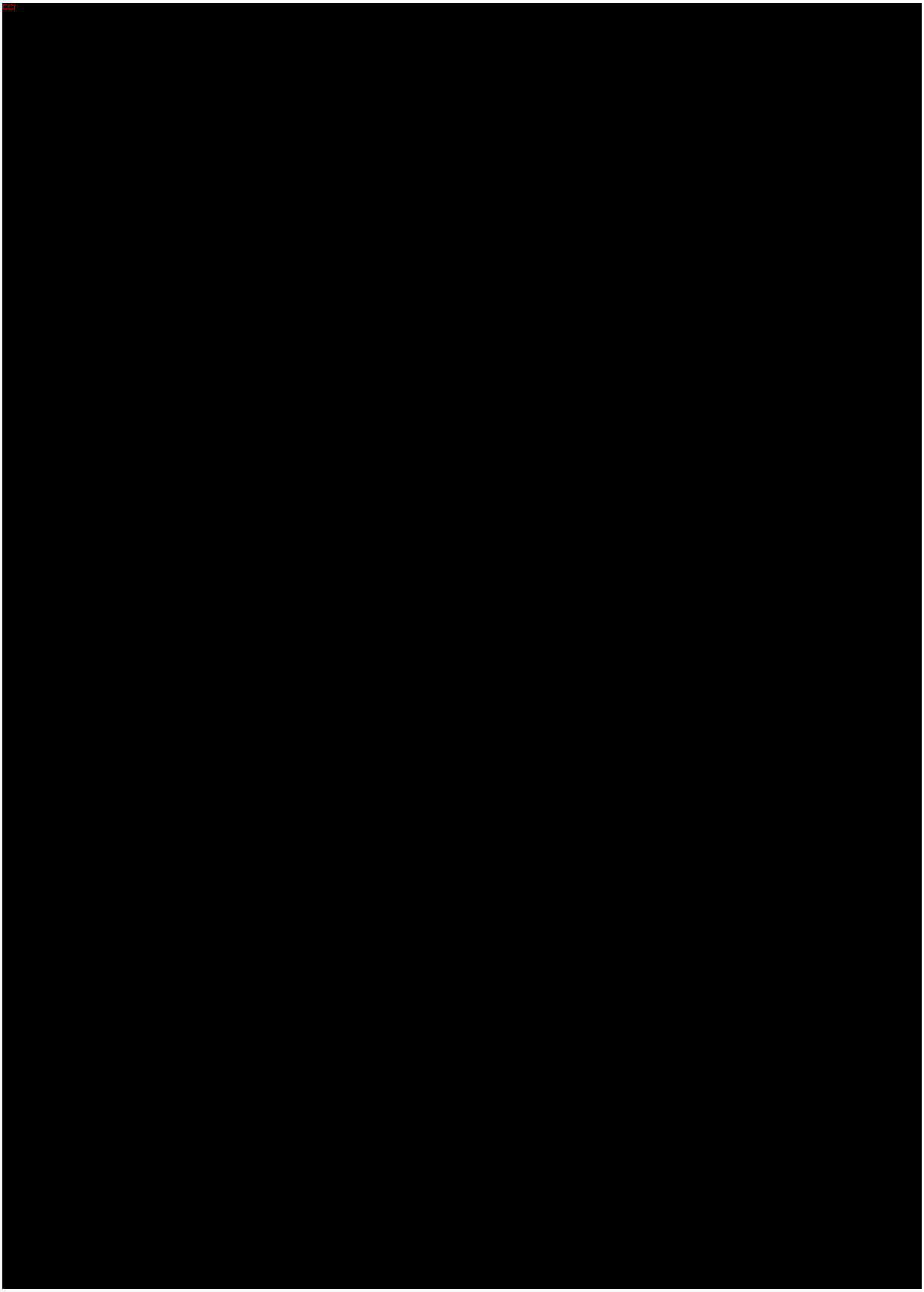
The EORTC QLQ-STO22 is a disease-specific questionnaire developed and validated to address measurements specific to gastric cancer. It is one of multiple disease-specific modules developed by the EORTC QLG designed for use in clinical studies, to be administered in addition to the QLQ-C30 to assess disease-specific treatment measurements. It contains 22 items with symptoms of dysphagia (4 items), pain or discomfort (3 items), upper GI symptoms (3 items), eating restrictions (5 items), emotional (3 items), dry mouth, hair loss, 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, selfcare, 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].

CCI

[redacted]



[redacted]

4.2.1.5 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

4.2.2.1 Rationale for 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 FP and CAPOX

Systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer as evidenced by treatment guidelines issued by the NCCN and ESMO [National Comprehensive Cancer Network 2013] [Cunningham, D. 2008].

Despite a large number of randomized studies, there is no globally accepted standard first-line chemotherapy regimen in HER2 negative, advanced, unresectable and/or metastatic gastric and GEJ adenocarcinoma. In general, combination chemotherapy regimens provide higher response rates than do single agents. Many patients are recommended to receive a fluoropyrimidine-platinum doublet over more toxic triplet chemotherapeutic regimens.

Platinum/fluoropyrimidine doublet regimens containing cisplatin or oxaliplatin and 5-FU or capecitabine are recognized worldwide as standard first-line chemotherapy regimens for

advanced, unresectable, and/or metastatic gastric and GEJ adenocarcinoma. These platinum/fluoropyrimidine doublet regimens are considered "preferred" by the NCCN Gastric Cancer Guideline committee [National Comprehensive Cancer Network 2016].

Most commonly used doublet regimens are XP, FP, CAPOX, and FOLFOX. Choices among these regimens are based on a patient's general medical condition and comorbidities in consideration of the different toxicity profiles of the regimens. This practice pattern is supported by global consensus guidelines regarding the treatment of advanced gastric cancer which recommend use of any of the doublets discussed above [National Comprehensive Cancer Network 2016] [Cunningham, D. 2008].

The current study will use FP or CAPOX as the standard-of-care backbone regimens. Investigators will have a choice between FP and CAPOX. Use of infusional 5-FU in this study provides an alternative fluoropyrimidine treatment to those participants unable to take oral capecitabine.

4.3 Justification for Dose

4.3.2 Justification for Chemotherapy "Backbone" Dose

FP Regimen

Dose determination for cisplatin and 5-FU in the FP regimen is in accordance with prescribing information for gastric cancer per their package inserts. In this study, the dose regimen will be cisplatin (80 mg/m^2) administered on Day 1 of each treatment cycle (Q3W) plus 5-FU (800 mg/m^2/day) administered as a continuous IV infusion from Day 1 to Day 5 of each treatment cycle (Q3W).

The safety and tolerability of pembrolizumab in combination with cisplatin and fluoropyrimidine (capecitabine or 5-FU) was evaluated in KEYNOTE-059 Cohort 2. Of the 18 participants treated, 64% were men, and the median age was 64 years old. There were no treatment-related deaths and only 3 participants (12%) discontinued treatment because of chemotherapy-related adverse events (stomatitis [Grade 3], hypoacusis [Grade 2], and increased creatinine level [Grade 1]); none of the AEs was considered by the investigator to be related to pembrolizumab [Wainberg, Z. A., et al 2017]. No participants discontinued treatment because of pembrolizumab-related AEs. Twenty-five participants (100%) experienced treatment-related AEs of any grade. Nineteen participants (76%) experienced Grades 3 to 4 treatment-related AEs; the most common treatment-related Grade 3 to 4 AEs were neutropenia, stomatitis, anemia, thrombocytopenia, decreased appetite, and fatigue. Immune-related AEs of any grade occurred in 12 participants (48%); the majority of these were Grades 1 to 2. The most common immune-mediated AEs were hypothyroidism and palmar-plantar erythrodysesthesias. There were no Grade 4 to 5 immune-mediated or infusion reactions. Based on these data, the combination of pembrolizumab, cisplatin, and fluoropyrimidine (capecitabine or 5-FU) has a manageable safety profile.

CAPOX Regimen

Dose determination for capecitabine and oxaliplatin in the CAPOX regimen is in accordance with prescribing information for gastric cancer per their package inserts. In this study, the dose regimen will be oxaliplatin (130 mg/m^2 IV) on Day 1 of each treatment cycle (Q3W) plus capecitabine (1000 mg/m^2 orally twice daily) on Days 1 to 14 of each treatment cycle (Q3W).

The combination of capecitabine, oxaliplatin, and pembrolizumab is currently being evaluated in multiple studies throughout the United States. In an investigator-initiated study conducted at Memorial Sloan Kettering Cancer Center in the United States (NCT02954536), pembrolizumab was combined with trastuzumab, oxaliplatin, and either 5-FU or capecitabine. This study was initiated in November 2016. Based on data from 18 participants dosed thus far, the combination appears safe, without dose-limiting toxicities or drug-related Grade 4 or Grade 5 AEs. The only drug-related Grade 3 events reported were hypokalemia (2), anemia (2), increased alanine aminotransferase (2), decreased lymphocytes (1), dehydration (1), nausea (1), maculopapular rash (1), diarrhea (1), and hyponatremia (1). None of the 18 participants has discontinued treatment due to therapy-related AEs. In addition, promising anticancer activity was observed, with 14 of 18 patients achieving objective responses (internal Merck data). A second investigator-initiated study at Duke (KeyLargo study) is a single-arm, Phase 2 study of the combination of pembrolizumab, oxaliplatin, and capecitabine in the first-line treatment of metastatic/recurrent adenocarcinoma of the esophagus or stomach. This study began enrolling participants in January 2018. The doses of capecitabine, oxaliplatin, and pembrolizumab used in the KeyLargo study are identical to those in this clinical study.

4.4 Beginning and End of Study Definition

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

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Male/Female participants with previously untreated, HER2 negative, advanced gastric or GEJ adenocarcinoma of at least 18 years of age will be enrolled in this study.

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

Sites in France, Germany, Japan, Italy, the Czech Republic and the UK should refer to Appendix 7, Country-specific Requirements, for clarifications regarding specific inclusion and exclusion criteria.

5.1 Inclusion Criteria

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

1. Has histologically- or cytologically-confirmed diagnosis of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma, with known PD-L1 expression status.

2. Has HER2 negative cancer.

   HER2 negative is defined as: IHC (0, or 1+) or FISH negative (HER2:CEP17 ratio <2 with an average HER2 copy number <4.0 signals/cell). FISH can be replaced with locally available ISH methods acceptable as per institutional guidelines (eg, DISH).

Demographics

3. Is Male or Female.

4. Is at least 18 years of age at the time of providing documented informed consent (or acceptable age according to local regulations, whichever is older).

Male Participants

5. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 95 days after the last dose of chemotherapy:

   • Refrain from donating sperm

   PLUS either:

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

   OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

- Agree to 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. 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-vaginal penetration.

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study drugs is more stringent than the requirements above, the local label requirements should be followed.

Female Participants

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

   - Is not a WOCBP

   OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 180 days after the last dose of chemotherapy or 120 days after the last dose of pembrolizumab, whichever is last, and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

   - A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours before the first dose of study intervention.

   - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

   - Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study drugs is more stringent than the requirements above, the local label requirements should be followed.

Informed Consent

7. The participant (or legally acceptable representative if applicable) provides written informed consent for the study. 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.

Additional Categories

8. Has measurable disease per RECIST 1.1 as assessed by investigator assessment. 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.

9. Has provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

   Note: If submitting unstained cut slides, newly cut slides should be received by the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).

10. Has provided tumor tissue sample deemed adequate for PD-L1 biomarker analysis.

    Note: Tumor PD-L1 expression status must be available prior to randomization.

11. Has provided tumor tissue sample for MSI biomarker analysis.

12. Has an ECOG performance status of 0 or 1 (within 3 days prior to the start of study intervention) (refer to Appendix 9).

13. Has adequate organ function, as defined in the following table (Table 4). Specimens must be collected within 10 days prior to the start-of-study intervention.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥60 mL/min for participant with creatinine levels >1.5 × institutional ULN Cisplatin and oxaliplatin product label should be followed for acceptable creatinine clearance rates. Participants are required to have a minimum creatinine clearance (CrCl) of 30 mL/min.
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Albumin	≥ 2.5 g/dL
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

Medical Conditions

1. Has squamous cell or undifferentiated gastric cancer.

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 intervention.

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

3. Has preexisting peripheral neuropathy >Grade 1.

4. Is a WOCBP who has a positive urine pregnancy test within 72 hours prior to randomization or treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

Prior/Concomitant Therapy

5. Has had previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Participants may have received prior neoadjuvant and/or adjuvant therapy as long as it was completed at least 6 months prior to randomization.

6. 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 coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

7. Has received prior systemic anticancer therapy including investigational agents within 4 weeks prior to randomization.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline.

8. Has received prior radiotherapy within 2 weeks prior to start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to noncentral nervous system (CNS) disease.

9. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention. Administration of killed vaccines is allowed.

Prior/Concurrent Clinical Study Experience

10. 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 intervention.

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

Diagnostic Assessments

11. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention.

12. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years.

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

13. 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 intervention.

14. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

15. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

16. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

17. Has an active infection requiring systemic therapy.

18. Has a known history of HIV infection.

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

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

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

20. Has a known history of active tuberculosis (TB; Bacillus tuberculosis).

21. Has a history or current evidence of any condition (eg, known deficiency of the enzyme dihydropyrimidine dehydrogenase), therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

22. Participants with hypokalemia (serum potassium less than the lower limit of normal).

23. Participants with hypomagnesemia (serum magnesium less than the lower limit of normal).

24. Participants with hypocalcemia (serum calcium less than the lower limit of normal).

25. Has a known psychiatric or substance abuse disorder that would interfere with the participant’s ability to cooperate with the requirements of the study.

Other Exclusions

26. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of chemotherapy or through 120 days after the last dose of pembrolizumab, whichever is last.

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

28. Has a known severe hypersensitivity (≥ Grade 3) to any of the study chemotherapy agents (including, but not limited to, infusional 5-fluorouracil or oral capecitabine) and/or to any of their excipients.

29. Grade ≥2 audiometric hearing loss.

    Note: For participants taking cisplatin.

5.3 Lifestyle Considerations

No lifestyle 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.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

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

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 5.

Table 5 Study Interventions

Group Name	Group Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	IMP/ NIMP	Sourcing
Pembrolizumab	Experimental	Pembrolizumab (MK-3475)	Biological/ Vaccine	Vial	25 mg/mL vial 100 mg vial	200 mg on Day 1 of each cycle (Q3W)	IV Infusion	Experimental	IMP	Provided centrally by the Sponsor
Placebo	Placebo Comparator	Placebo (refer to Pharmacy Manual)	Drug	Solution for infusion	N/A	On Day 1 of each cycle (Q3W)	IV Infusion	Placebo	IMP	Provided locally by the study site, subsidiary, or designee
FP Backbone Chemotherapy										
Cisplatin	Other	Cisplatin	Drug	Ampule	1 mg/mL vial 20 mg vial or 50 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	Other	5-FU	Drug	Ampule	25 mg/mL vial 50 mg/mL vial	800 mg/m^2/day continuous on Days 1 to 5 of each cycle (120 hours, or per local standard) (Q3W)	IV Infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee

Group Name	Group Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	IMP/ NIMP	Sourcing
CAPOX Backbone Chemotherapy										
Oxaliplatin	Other	Oxaliplatin	Drug	Ampule	5 mg/mL vial 50 mg vial or 100 mg vial	130 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
Capecitabine	Other	Capecitabine	Drug	Tablet	150 mg tablet 500 mg tablet	1000 mg/m^2 twice daily on Days 1 to 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

5-FU=5-fluorouracil; CAPOX=capecitabine and oxaliplatin; FP=cisplatin and 5-fluorouracil; IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product; Q3W=every 3 weeks

Definition Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP) is 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.

* Duration of cisplatin or oxaliplatin treatment may be capped at 6 cycles as per local country guidelines. Treatment with 5-FU/capecitabine may continue per protocol.

Investigator decision regarding the type of backbone chemotherapy (FP or CAPOX) should be determined prior to randomization.

Participants should continue on the type of backbone chemotherapy chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor.

Participants who are randomized to placebo are not allowed to crossover to pembrolizumab treatment.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 5 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 6.1.1 for details regarding administration of the study intervention.

Refer to Section 8.1.8.1 for details regarding the order of administration of study intervention.

A cycle of treatment is 3 weeks (21 days) long and is set relative to pembrolizumab/placebo.

Use of nonexperimental standard-of-care chemotherapies and supportive medications should follow the appropriate package insert and locoregional practice guidelines, as mandated by local health regulatory agencies. Please consult the specific appendix, where appropriate.

6.1.1 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 will 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 between infusion pumps, 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 prepared by the unblinded pharmacist (refer to the Pharmacy Manual). The placebo will be dosed and administered by blinded and qualified study site personnel in the same manner as the investigational product (pembrolizumab).

6.1.2 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. Duration of cisplatin treatment may be capped at 6 cycles as per local country guidelines.

5-fluorouracil 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 SoA in Section 1.3.

Investigators are advised to counsel participants assigned to receive 5-FU about risk of photosensitivity and to take sun protection measures accordingly. Participants receiving cisplatin should be monitored for audiological complications (Section 8.3.1.3).

6.1.3 CAPOX

Oxaliplatin 130 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.

Capecitabine will be administered orally as a 1000 mg/m^2 dose twice daily from Day 1 to Day 14 of each treatment cycle. The evening dose of capecitabine should be taken approximately 12 hours after the morning dose. Capecitabine should be taken with food, or within 30 minutes after food/meal, with approximately 200 mL of water. Sites may follow local practice patterns regarding calculation of capecitabine milligram dose. Refer to the product label for additional guidance on administration procedures for capecitabine.

Note: If the participant is enrolled later in the day, it is acceptable for the first dose to be taken on Day 1, and twice daily dosing can continue on Days 2 to 14; 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. Participants receiving capecitabine should be carefully monitored for ophthalmological complications and skin reactions (Section 8.3.1.4).

6.1.4 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Dose preparation must be done by separate unblinded study personnel. Dose administration must be done by blinded study personnel.

Concomitant chemotherapeutic/immunotherapeutic agents will be prepared and administered as per the approved product label(s). The BSA in m^2 should be calculated per local guidance. The dose of oxaliplatin and cisplatin shall not be recalculated by body weight fluctuation in principle, but for 10% or higher fluctuation of body weight, recalculation is possible at the discretion of the investigator. When recalculating, 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 intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. For those study interventions taken home, the participant must be instructed on appropriate storage and handling, per the label.

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

6.3.2 Stratification

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

1. Geographical region
    - Europe/Israel/North America/Australia
    - Asia
    - Rest of the World (including South America)
2. PD-L1 tumor expression status (CPS <1, ≥1)
3. Combination chemotherapy (FP, CAPOX)

6.3.3 Blinding

A double-blinding technique will be used. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant and the investigator who is involved in the study intervention administration or clinical evaluation of the participants are unaware of the group assignments.

6.4 Study Intervention Compliance

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

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.2 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruption of pembrolizumab.

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

6.5 Concomitant Therapy

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 intervention may be required. The investigator is to discuss prohibited medication with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study

intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab.
- Radiation therapy.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion and, if possible without compromising participant safety, after consultation with the Sponsor.

- Live or live-attenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Administration of killed vaccines is allowed.
- 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. The use of systemic steroids at a dose >10 mg/day of prednisone (or equivalent) may be approved after consultation with the Sponsor.

  Note 1: For the purpose of preventing chemotherapy-induced nausea/vomiting, the administration of dexamethasone should be limited to those instances when the participant is receiving high (or moderate) emetic risk chemotherapy. The dose and duration of dexamethasone administration should be limited to the lowest needed to prevent and/or treat chemotherapy-related nausea and emesis.

  Note 2: Antiemetic prophylaxis with corticosteroids per NCCN or institutional guideline is permitted.

- For participants receiving 5-FU or capecitabine:

  - Brivudine, Sorivudine analogs, and other inhibitors of the enzyme DPD.

- For participants receiving cisplatin:
  - Phenytoin should not be started with cisplatin therapy.

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.

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.
- Drugs known to prolong the QTc interval should be used with caution. Please refer to the website https://www.crediblemeds.org prior to administration of 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 eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and events of clinical interest (ECIs) are defined in Section 8.4.7.

6.5.1 Rescue Medications and Supportive Care

6.5.1.1 Supportive Care Guidelines for Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 6 and Table 7 in Section 6.6.2 for guidelines regarding dose modification and supportive care.

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

6.5.1.2 Supportive Care Guidelines for Combination Therapy

6.5.1.2.1 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 on Day 1, 80 mg on Day 2, 80 mg on 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 to 4 times per day

Additionally, use of steroids for cisplatin associated antiemetic support is allowed and is to follow the NCCN or institutional guidelines. However, caution must be exercised to prevent the overuse of steroids. For the purpose of preventing chemotherapy-induced nausea/vomiting, the administration of dexamethasone should be limited to those instances when the participant is receiving high (or moderate) emetic risk chemotherapy. The dose and duration of dexamethasone administration should be limited to the lowest needed to prevent and/or treat chemotherapy-related nausea and emesis.

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

6.5.1.2.2 Supportive Care Guidelines for 5-FU

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

6.5.1.2.3 Supportive Care Guidelines for Capecitabine

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

6.5.1.2.4 Supportive Care Guidelines for Oxaliplatin

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

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Initial Treatment or First Course

The Initial Treatment or First Course of pembrolizumab consists of 35 treatments. Note: The number of treatments is calculated starting with the first dose. Participants who stop the

combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study intervention provided they meet the requirements detailed in Section 8.13.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

For participants who have attained a confirmed CR and have received at least 2 doses of pembrolizumab monotherapy and been treated for at least 8 cycles (at least 24 weeks) or received 2 cycles of the combination including 2 doses of pembrolizumab or matching placebo and at least 80% of the planned doses of combination chemotherapy beyond the date when the initial CR was declared, the treatment may be stopped. These participants may be eligible for Second Course described in Section 6.7.

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

The investigator may attribute each toxicity event to oxaliplatin, cisplatin, 5-FU, capecitabine, or pembrolizumab/placebo alone and use a stepwise dose reduction according to Table 6 and Table 7 (pembrolizumab), Table 8 (CAPOX), Table 9 (oxaliplatin), Table 10 (capecitabine), Table 11 (FP), Table 12 (cisplatin), and Table 13 (5-FU). 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 intervention.
- Pembrolizumab/placebo dose reductions are not permitted. Pembrolizumab/placebo treatment may be interrupted or discontinued due to toxicity.
- If a dose reduction for toxicity occurs with any study intervention, the dose may not be reescalated.
- Participants can have a maximum of 3 dose modifications to oxaliplatin and 2 dose modifications to infusional 5-FU, capecitabine, and cisplatin for drug-related toxicities 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 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 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/placebo should be interrupted or discontinued according to the recommended dose modifications.

- Both groups may have chemotherapy discontinued and continue to receive pembrolizumab/placebo.

The CTCAE version 4.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 6 and Table 7 (pembrolizumab), Table 8 (CAPOX), Table 9 (oxaliplatin), Table 10 (capecitabine), Table 11 (FP), Table 12 (cisplatin), and Table 13 (5-FU). 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 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 6 and Table 7 (pembrolizumab) and Section 6.5.1.

6.6.2.1 Dose Modification 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 AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

Table 6 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.
	Recurrent Grade 3 or 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	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New 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 liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

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**
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 but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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 7.

Table 7 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 drug treatment.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention 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 drug treatment.	No subsequent dosing
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 Common Terminology Criteria for Adverse Events v4.0 (CTCAE) 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.

6.6.2.2 Dose Modification for Combination Chemotherapy

Dose modifications for CAPOX combination, oxaliplatin, and capecitabine are detailed in Table 8, Table 9, and Table 10, respectively. Dose modifications for FP combination, cisplatin, and 5-FU are detailed in Table 11, Table 12, and Table 13, respectively. 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.

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.

Table 8 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 twice daily	750 mg/m^2 twice daily	500 mg/m^2 twice daily	Discontinue	Discontinue

Table 9 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[a]	Neutropenia[b]	2-3[c]	Neutrophil count resolves to ≥1,500/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[c]	Neutrophil count resolves to ≥1,500/mm^3	Reduce by 1 DL	If >3 DL reductions exceeded
	Febrile Neutropenia	3[c]	Toxicity resolves	Reduce by 1 DL	If >3 DL reductions exceeded
		4[c]	n/a	Discontinue	Permanently discontinue oxaliplatin
	Thrombocytopenia	3-4[c]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL[d]	If >3 DL reductions exceeded
Non-hematologic[a]	Creatinine Increased	≥1.5 mg/dL[c]	<1.5 mg/dL	No reduction	If >3 DL reductions exceeded
	Peripheral Sensory Neuropathy[e]	3-4[c]	Grade 0-2	Reduce by 1 DL	If >3 DL reductions exceeded
	All Other Non-hematologic Toxicities[a]	3-4[c]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >3 DL reductions exceeded
	Laboratory Adverse Events[f]	3-4[c]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >3 DL reductions exceeded

Category	Toxicity	Hold Oxaliplatin Treatment for Grade	Timing for Restarting Oxaliplatin Treatment	Dose for Restarting Oxaliplatin Treatment	Discontinue Oxaliplatin

AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor; n/a=not applicable

[a] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
[b] See the package insert of each of the G-CSF drugs for administration of G-CSF for neutropenia.
[c] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.
[d] Dose reduction at Grade 3 is at the discretion of the investigator but not required.
[e] Administration may be interrupted or reduced at the discretion of the investigator.
[f] Allow continuous treatment for laboratory AEs that are asymptomatic and deemed to be not clinically significant.

Table 10 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[a]	Neutropenia	3[b]	Neutrophil count resolves to >1,000/mm^3	No Reduction *consider G-CSF	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
		4[b]	Neutrophil count resolves to >1,000/mm^3	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
	Febrile Neutropenia	3[b]	Toxicity resolves	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
		4[b]	n/a	Discontinue	Permanently discontinue
	Thrombocytopenia	3-4[b]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded

Category	Toxicity	Hold Capecitabine Treatment for Grade	Timing for Restarting Capecitabine Treatment	Dose for Restarting Capecitabine Treatment	Discontinuation of Capecitabine
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 oral intake or if >2 DL reductions exceeded
		4	n/a	Discontinue	Permanently discontinue
	All Other Non-hematologic Toxicities[c]	3-4[b]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
	Laboratory Adverse Events[d]	4[b]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded

AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor; n/a=not applicable

[a] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
[b] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.
[c] 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.
[d] Allow continuous treatment for laboratory AEs that are asymptomatic and deemed to be not clinically significant.

Table 11 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 12 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[a]	Neutropenia	3[b]	Neutrophil count resolves to >1,000/mm^3	No Reduction *consider G-CSF	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
		4[b]	Neutrophil count resolves to >1,000/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[b]	Toxicity resolves	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
		4[b]	n/a	Discontinue	Permanently discontinue cisplatin
	Thrombocytopenia	3-4[b]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
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[b]	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[b]	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[b]	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[c]	3-4[b]	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[d]	4[b]	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

AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor; n/a=not applicable

[a] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
[b] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.
[c] 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.
[d] Allow continuous treatment for laboratory AEs that are asymptomatic and deemed to be not clinically significant.

Table 13 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[a]	Neutropenia	3[b]	Neutrophil count resolves to >1,000/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[b]	Neutrophil count resolves to >1,000/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[b]	Toxicity resolves	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
		4[b]	n/a	Discontinue	Permanently discontinue
	Thrombocytopenia	3-4[b]	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
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	n/a	Discontinue	Permanently discontinue
	All Other Non-hematologic Toxicities[c]	3-4b[b]	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[d]	4[b]	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

AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor; n/a=not applicable

[a] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
[b] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.
[c] 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.
[d] Allow continuous treatment for laboratory AEs that are asymptomatic and deemed to be not clinically significant.

6.7 Second Course Phase (Pembrolizumab)

All participants who stop study intervention 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 study intervention from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

EITHER

- Stopped initial study intervention after attaining an investigator determined confirmed CR based on RECIST 1.1, and
  - Was treated with at least 8 cycles of study intervention 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 study intervention after completion of 35 administrations (approximately 2 years) of study intervention for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
  - Upon unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
  - No new anticancer treatment was administered after the last dose of study intervention, 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 study 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 study.

6.8 Intervention After the End of the Study

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

6.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity . The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Refer to Section 8.1.10 for a description of the method of unblinding a participant during the study should such action be warranted.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 (SoA) and Section 8.13.3.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Unacceptable adverse events as described in Appendix 3.

- The participant interrupts pembrolizumab administration for more than 12 consecutive weeks unless written 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 intervention.
- Noncompliance with study treatment or procedure requirements.
- The participant has a confirmed positive serum pregnancy test.
- Prohibited concomitant medication requiring withdrawal (refer to Section 6.5).
- Confirmed radiographic disease progression outlined in Section 8.13 (exception if the Sponsor approves treatment continuation)
- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment
- Recurrent Grade 2 pneumonitis

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

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

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

The maximum amount of blood collected from each participant at each treatment cycle/visit will be approximately 6.0 mL to 48.0 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 or the participant's legally acceptable representative , answer all of his/her questions, and obtain documented 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 used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

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

8.1.4 Medical History

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

8.1.5 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 first dose. 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. Concomitant medications will be recorded for 30 days after the last dose of study intervention (or longer if related to an SAE or ECI). In addition, new medications started during the Second Course through the Second Course Safety Follow-up Visit should be recorded.

8.1.6 Assignment of Screening Number

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

Any participant who is rescreened 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 8.13.1.3.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

Study intervention should begin within 3 days after randomization.

8.1.8.1 Timing of Dose Administration

Study intervention in both groups will begin on Day 1 of each 3-week dosing cycle after all procedures/assessments have been completed, as detailed in Section 1.3 (SoA). Study interventions may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (except Cycle 1, which may be administered up to 3 days after the scheduled Day 1).

All study interventions may be administered on an outpatient basis.

Study interventions will be administered in the order presented below:

1. Pembrolizumab or placebo infusion
2. Cisplatin or oxaliplatin infusion
3. 5-FU infusion or capecitabine

Refer to Section 6.1 for details on study intervention administration.

Refer to Section 6.6 for information on allowed dosing interruptions.

Refer to Section 7 for criteria for discontinuation of study intervention.

Refer to Section 6.7 for details of Second Course pembrolizumab therapy.

8.1.9 Discontinuation and Withdrawal

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

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

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 intervention, 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.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

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.

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

1. For the welfare of the participant, if necessary.

2. Participants requiring Second Course who completed 35 cycles and stopped first course study intervention with SD or better and has to discontinue for any reason other than disease progression, intolerability, or CR (per protocol requirement). Such participants must have experienced radiographic disease progression while off study intervention according to the criteria in Section 6.7.

Every effort should be made to avoid unblinding. 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 until the study is completed.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee 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.

8.1.11 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

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

The process for scan collection and transmission to the iCRO can be found in the Site Imaging Manual. Tumor scans are strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Magnetic resonance imaging is the strongly preferred modality for imaging the brain. The same scan 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 scans.

In general, scans should include the chest, abdomen, and pelvis.

Note: for the purposes of assessing tumor scans, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Participant eligibility will be determined using investigator assessment. All scheduled scans for all participants from the sites will be submitted to the iCRO. In addition, scans (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as scans obtained for other reasons, but which demonstrates radiologic progression, should also be submitted to the iCRO.

When the investigator identifies disease progression, the iCRO will verify this progression and email the results to the study site and Sponsor (Section 8.2.1.5 and Figure 2). In clinically stable participants, scans are to continue until disease progression has been verified by BICR. If initial investigator-assessed progression was not verified by BICR, each subsequent scan must be submitted to the iCRO. Once progression is verified by BICR, subsequent scans (if acquired) should not be submitted to the iCRO.

8.2.1.1 Initial Tumor Scans

The screening scans must be submitted to the iCRO for retrospective review.

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

8.2.1.2 Tumor Scans During the Study

The first on-study imaging assessment should be performed at 6 weeks (42 days +7 days]) from the date of randomization. Subsequent tumor scans should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Scans are to be performed until disease progression is identified by the investigator and verified by BICR, the start of new anticancer treatment, withdrawal of consent, or death.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

When radiological disease progression is identified by the investigator in clinically stable participants, disease progression is to be confirmed by another set of scans performed 4 to 8 weeks later, per iRECIST guidelines Section 8.2.1.6.

If disease progression is not confirmed, clinically stable participants are to continue study intervention until progression is confirmed. Participants are to return to their regular scan schedule. If the next scheduled scan will occur in less than 4 weeks, this scheduled scan may be skipped.

If disease progression is confirmed, study intervention will be discontinued. Exceptions are detailed in Section 8.2.1.6.

8.2.1.3 End-of-Treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4 week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization (refer to Section 8.2.1.2).

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

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

- withdrawal of consent
- the end of the study

Participants who are clinically stable and treated past radiographic progression may continue to be assessed until progression is confirmed according to the rules of iRECIST, when clinically appropriate.

8.2.1.4 Second Course (Retreatment) Tumor Scans

Tumor scans must be performed within 28 days prior to restarting study intervention with pembrolizumab. If disease progression has been verified by BICR for the First Course, the Second Course may be initiated. The disease progression scan may be used as the Second Course baseline scan if performed within 4 weeks prior to dosing and meets the scan standards.

The first scan should be performed at 6 weeks (42 days +7 days) after the restart of study intervention. Subsequent tumor scans are to be performed every 6 weeks (42 days ±7 days) or more frequently, if clinically indicated.

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

If participants discontinue study intervention, tumor scans are to be performed at discontinuation (±4 week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor their disease status by acquiring tumor scans every 6 weeks (42 days ±7 days) until the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

Response assessments and progressive disease are determined by investigator site assessment. only.

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

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 intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

The initial tumor scan showing site-assessed disease progression should be submitted immediately to the iCRO for BICR verification of disease progression. The site will be notified if the iCRO verifies disease progression using RECIST 1.1. Figure 2 illustrates the scan flow involving verification of disease progression 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 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

Any participant deemed clinically unstable should be discontinued from study intervention 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 intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the iCRO 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 intervention may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study intervention.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 (SoA) and submitted to the iCRO.

A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 14 and illustrated as a flowchart in Figure 2.

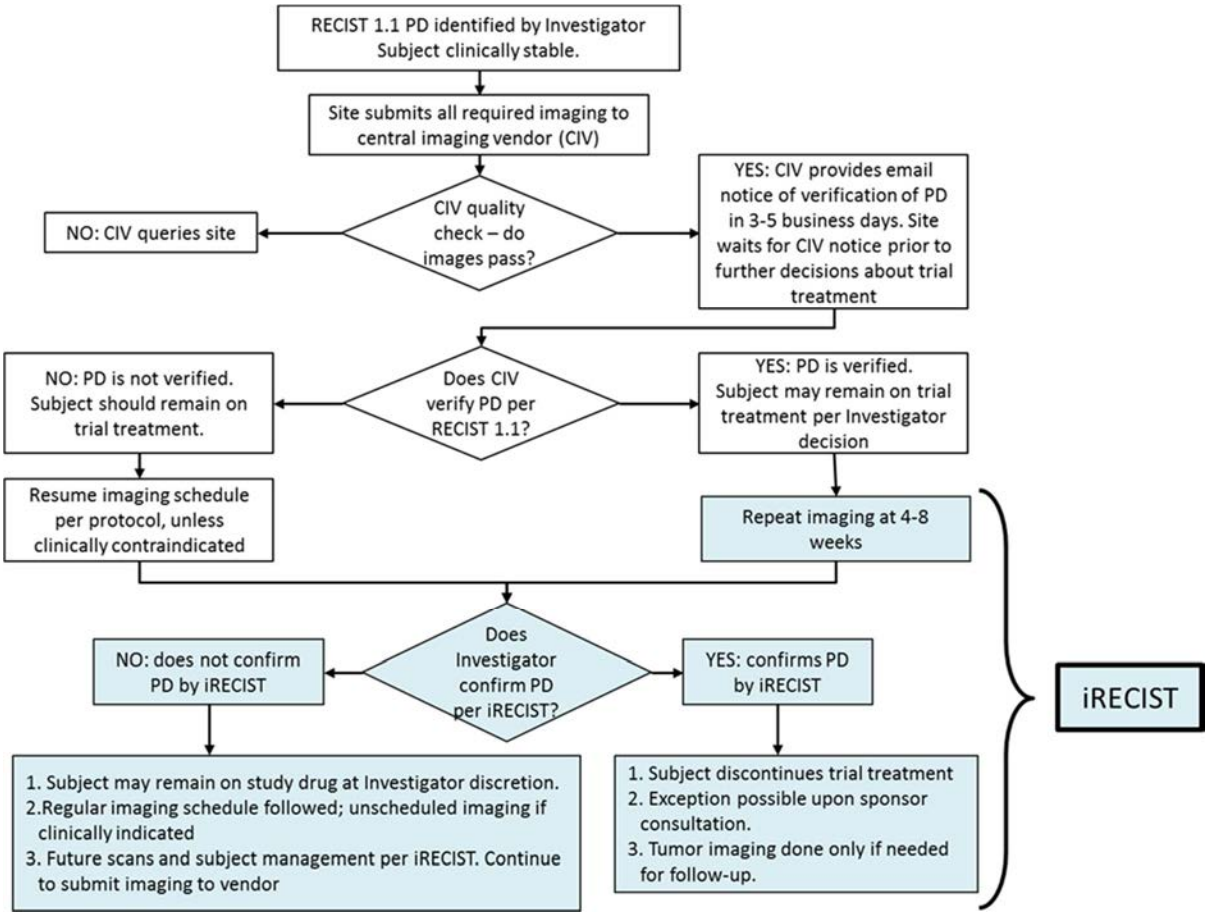
Table 14 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	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 intervention at the assessment of the investigator and after the participant's reconsent.	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 intervention 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 intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

BICR=blinded independent central review; 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

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 iCRO, 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 iCRO with verification of progression request until RECIST 1.1 progression is verified by BICR.



CIV=central imaging vendor (ie, iCRO); iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1

Figure 2 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 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, then EORTC QLQ-STO22. The questionnaires should be administered prior to dosing at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, and every 2 cycles thereafter (eg, Cycle 7, Cycle 9, etc.), at the Treatment Discontinuation Visit, and at the 30-day Safety Follow-up Visit. A visit window of ± 7 days will apply to PRO visit assessments.

It is best practice and strongly recommended that electronic patient-reported outcomes (ePROs) are administered to randomized participants prior to drug administration, AE 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. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Study Procedures Manual.

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

8.3.1 Physical Examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

The investigator or medically qualified designee (consistent with local requirements) will perform a complete physical examination per institutional standards during the screening period. Height and weight will also be measured and recorded. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examinations are described in Section 1.3 (SoA). After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination, as defined in Section 1.3 (SoA), the investigator or medically qualified designee (consistent with local requirements) will perform a directed physical examination per institutional standards prior to the administration of the study intervention. New clinically significant abnormal findings should be recorded as AEs.

8.3.1.3 Audiometry (Only in Participants Receiving Cisplatin)

In participants receiving cisplatin, audiometry testing will be performed at screening by the investigator or medically qualified designee (consistent with local requirements). Assessments may be repeated during the study, as clinically indicated. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.4 Additional Monitoring (Only in Participants Receiving Capecitabine)

Participants receiving capecitabine 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.

Capecitabine can induce severe skin reactions such as SJS and TEN. Capecitabine should be permanently discontinued in participants who experience a severe skin reaction during treatment.

After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

Vital signs (temperature, pulse rate, respiratory rate, and blood pressure) will be assessed by the investigator or medically qualified designee (consistent with local requirements) as specified in Section 1.3 (SoA). After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at screening. Clinically significant abnormal findings should be recorded as medical history. Assessments may be repeated during the study, as clinically indicated.

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

8.3.4 Clinical Safety Laboratory Assessments (Hematology, Chemistry and Urinalysis)

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and Section 1.3 (SoA).

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

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

Details regarding specific laboratory 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 the Study Procedures Manual.

Refer to Section 1.3 (SoA) for the timing of laboratory assessments.

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.5 Pregnancy Test

Pregnancy testing ([urine or serum] as required by local regulations) should be conducted according to Section 1.3 (SoA) and at the end of relevant systemic exposure for all arms.

- Pregnancy testing requirements for study inclusion are described in Section 5.1.

- Pregnancy testing ([urine or serum] as required by local regulations) should be conducted at monthly intervals during intervention.

- Pregnancy testing ([urine or serum] as required by local regulations) should be conducted for at least 30 days after the last dose of study intervention.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or medically qualified designee (consistent with local requirements) will assess ECOG status (see Appendix 9) at the time points specified in Section 1.3 (SoA).

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

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

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

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

- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 180 days following the last dose of chemotherapy or through 120 days following the last dose of pembrolizumab, whichever is greater, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 15.

Table 15 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event:	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Timeframe to Report Event and Follow-up Information to Sponsor:**
Nonserious 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: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy.

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

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

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

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

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

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose) for pembrolizumab and an as any dose exceeding the prescribed dose by ≥20% for other study treatments.

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.

Treatment of overdose of other study treatments should follow the prescribed information in the relevant package insert.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

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

- Leftover DNA
- 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 Planned MSI Analysis Sample Collection

MSI will be evaluated as this is an important biomarker for gastric cancer. Both tumor tissue samples and blood will be collected for MSI analyses and are required to perform central MSI testing by PCR. In order to perform MSI analysis by PCR, blood and tumor tissue is required. A blood sample is collected to extract normal DNA for comparison testing to tumor DNA in MSI analysis.

The rationale underlying the necessity to assess MSI status in participants enrolled in the study emanates from a clinical study that showed mismatch repair status predicts clinical benefit of immune checkpoint blockade with pembrolizumab.

8.10 Planned Genetic Analysis Sample Collection

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or

local IRB/IEC does not approve) sample collection for these purposes, then such samples are not to be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for FBR only if participant signs the FBR consent.

8.11 Biomarkers

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

- Blood for Genetic Analyses
- Blood for ctDNA Analyses
- Blood for RNA analyses
- Blood for plasma biomarker analysis
- Blood for serum biomarker analysis
- Archival or newly obtained tissue collection

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

Biomarker sample collection for participants enrolled in China will be dependent on approval by the Human Genetic Resources Administration of China.

8.12 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency room visits must be reported in the electronic case report form (eCRF), from the time of treatment allocation/randomization through 90 days following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.13 Visit Requirements

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

8.13.1 Screening

8.13.1.1 Prescreening Period

The Prescreening Period may be utilized to determine biomarker eligibility based on HER2 and PD-L1 expression status using an archival tumor biopsy sample. An archival tissue sample taken up to 1 year prior to study randomization is preferred. After signing an authorization form for release of tumor tissue, participants will be assigned a screening

number. Characterization of HER2 and PD-L1 status will be performed at a prescreening visit for participants with an available archival tumor biopsy sample. If the participants are HER2 negative, 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 prescreening Period as eligibility based on HER2 expression status will be determined in the main study screening period.

8.13.1.2 Screening Period

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

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

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

If a site decides to rescreen a participant more than once, a Sponsor consultation will be required.

8.13.2 Treatment Period

Visit requirements are outlined in Section 1.3 (SoA). Specific procedure-related details are provided in Section 8.1 through Section 8.13. Unless otherwise specified, assessments/procedures are to be performed prior to administration of study intervention. Unless otherwise specified, the window for each visit is ± 3 days.

8.13.3 Discontinued Participants Continuing to be Monitored in the Study

8.13.3.1 Safety Follow-up Visit

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

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

8.13.3.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up and should be assessed every 6 weeks (42 days ± 7 days) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, withdrawal of consent, pregnancy, end of study, or if the participant begins retreatment with pembrolizumab, as detailed in Section 6.7. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.7 will move from Efficacy Follow-up to Second Course when they experience disease progression. Details are provided in Section 1.3 (SoA) for retreatment with pembrolizumab.

8.13.3.3 Survival Follow-up Assessments

Participant Survival Follow-up contact will occur approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first Survival Follow-up assessment should be scheduled as described below:

1. For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first Survival Follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).

2. For participants who completed assessments in Efficacy Follow-up, the first Survival Follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.13.4 Vital Status

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

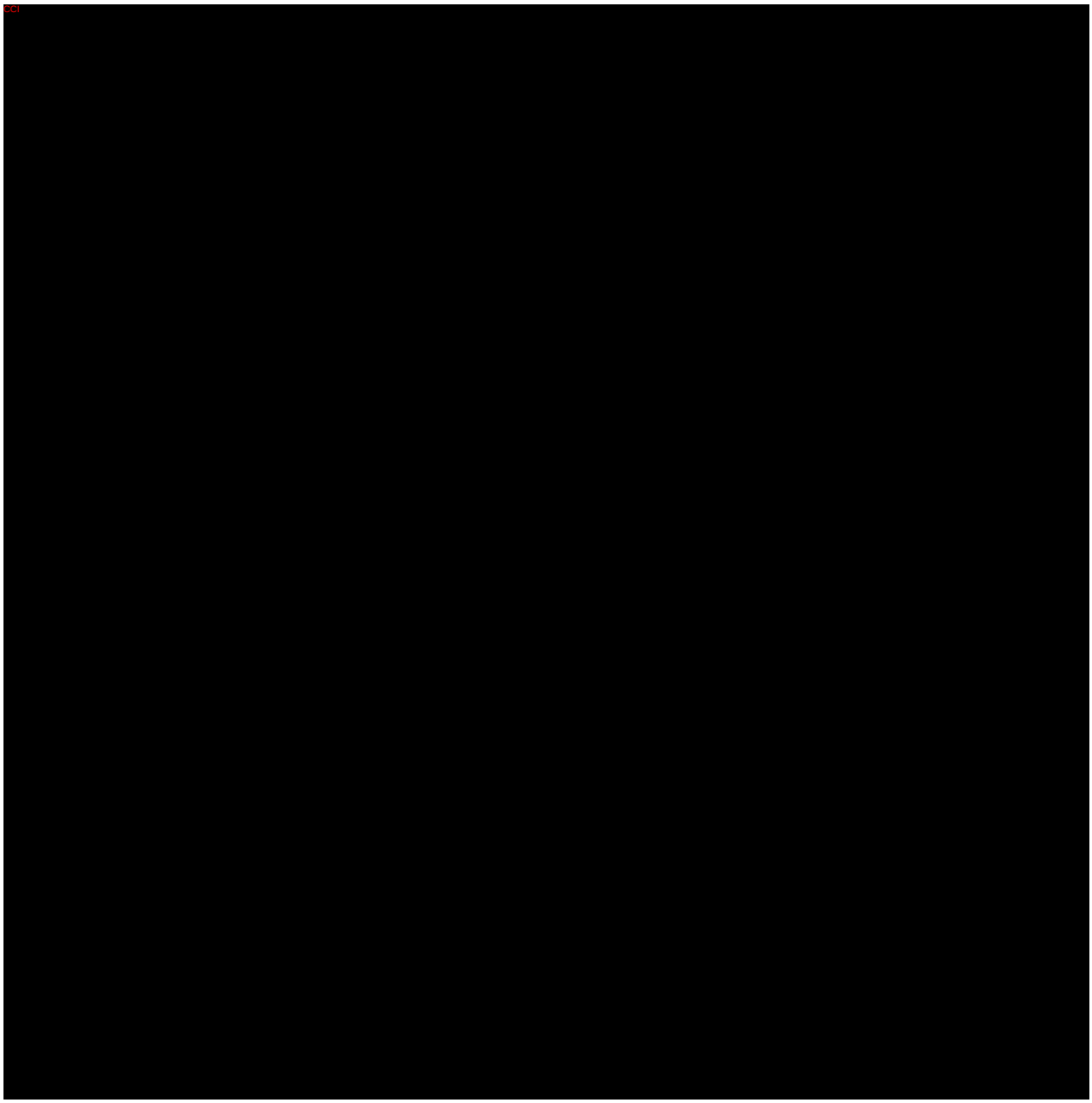
9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. 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 nonconfirmatory analyses made after the protocol has been finalized will be documented in an 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.

Details pertaining to the statistical analyses for participants who will be potentially enrolled in a possible China extension will be provided in a separate section of sSAP.

9.1 Statistical Analysis Plan Summary

Study Design Overview	This is a A Phase 3, randomized, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-859)
Treatment Assignment	Participants will be randomized in a 1:1 ratio to the experimental group and the control group. Stratification factors are described in Section 6.3.2.
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoint	OS
Key Secondary Endpoints	PFS per RECIST 1.1 assessed by BICR OR per RECIST 1.1 assessed by BICR
Statistical Methods for Key Efficacy Analyses	The hypotheses on PFS and OS will be evaluated by comparing the experimental group to the control group using a stratified log-rank test. The hazard ratio (HR) 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 M&N 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 M&N method [Miettinen, O. 1985].



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 intervention assignment.

Blinding issues related to the planned interim analysis 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

Primary

- **Overall Survival (OS)**

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

Secondary

- **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.

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

  OR defined as a CR)or a PR.

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

  For participants who demonstrated CR or PR, 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 and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory values, and vital signs.

9.4.3 Patient-reported Outcome (PRO) Endpoint

The PRO endpoints (eg, score change from baseline over time), which include EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D-5L scores, are described in Section 3. Details will be provided in the sSAP.

9.5 Analysis Populations

Extension Portion of the Study in China

After the sample size required for the Global portion is reached, the study may remain open to randomize participants in China until the sample size for the Chinese participants meets the target for China. The Chinese participants randomized after the enrollment of the Global portion is closed will not be included in the primary analysis population which is based on the Global portion. The China portion will also be analyzed separately per local regulatory requirement.

9.5.1 Efficacy Analysis Populations

The 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.

The ITT CPS ≥10 population in the primary analysis will include participants whose CPS ≥10 status can be determined from 3 sources: 1) Participants are prospectively identified as having tumors with CPS ≥10 at enrollment; 2) Participants with archived specimens are rescored and determined to be CPS ≥10 retrospectively; and 3) Participants who could not be rescored at CPS10 cutoff retrospectively are categorized as CPS ≥10 based on raw scores from testing at study entry.

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 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the study intervention group to which they are randomized. Participants who receive incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives the incorrect study intervention for 1 or more cycles but receives the correct study intervention 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 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study intervention 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. Response or progression in the Second Course will not count toward the PFS/ORR analyses in this study.

9.6.1.1 Overall Survival

The nonparametric 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, 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 6.3.2) 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 last known alive date.

In the CPS ≥10 population, to evaluate whether treatment effect could be impacted by different methods to determine CPS ≥ 10 status, a sensitivity analyses of OS will be performed for 3 subgroups: 1) Participants are prospectively scored at CPS ≥10 at enrollment; 2) Participants with archived specimens are rescored and determined to be CPS ≥10 retrospectively; and 3) Participants who could not be rescored at CPS≥10 cutoff retrospectively are categorized as CPS ≥10 based on raw scores from testing at study entry if sample size is sufficient large.

9.6.1.2 Progression-free Survival

The nonparametric 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 groups. 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 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the 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. In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 1 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) occur immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer 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 anticancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than complete response to be a PD event for participants without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 16.

Similar to the sensitivity analysis for OS endpoint, additional sensitivity analyses of PFS in CPS ≥10 population will be also considered to evaluate whether treatment effect could be impacted by different methods to determine CPS ≥10 status.

Table 16 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 anticancer 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 anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer 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 intervention or completed study intervention
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

PD=progressive disease; PFS=progression-free survival

9.6.1.3 Objective Response Rate

The stratified M&N method will be used for the comparison of the ORR between the 2 treatment groups. The difference in ORR and its 95% CI from the stratified M&N method with strata weighting by sample size will be reported [Miettinen, O. 1985]. The stratification factors used for randomization (Section 6.3.2) will be applied to the analysis.

9.6.1.4 Analysis Strategy for Key Efficacy Endpoints

Table 17 summarizes the primary analysis approach for key efficacy endpoints.

Table 17 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method [a]	Analysis Population	Missing Data Approach
Primary Endpoint			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥10, CPS ≥1, and all participants)	Censored at the last known alive date
Key Secondary Endpoints			
PFS per RECIST 1.1 by BICR	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥10, CPS ≥1, and all participants)	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are provided in Table 16, Censoring Rules for Primary and Sensitivity Analyses of PFS)
ORR per RECIST 1.1 by BICR	Test and Estimation: Stratified M&N method with sample size weight	ITT (CPS ≥10, CPS ≥1, and all participants)	Participants without assessments are considered nonresponders and conservatively included in the denominator

BICR=blinded independent central review; CPS=combined positive score; ITT=Intention to Treat; M&N=Miettinen and Nurminen; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors

a. Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 6.3.2) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach as shown in Table 18. 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 adverse events 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 groups 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 populations enrolled in this study are in critical condition 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 AE (≥5% of participants in one of the treatment groups) and SAE (≥5% of participants in one of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences. These analyses will be performed using the M&N method, an unconditional, asymptotic method [Miettinen, O. 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 table format.

Table 18 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 both the treatment groups)		X
	Discontinuation due to AE		X
	Change from baseline results (laboratory test toxicity grade)		X

AE=adverse event; CI=confidence interval; SAE=serious adverse event
X = results will be provided.

9.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline 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, and the primary reasons for screening failure and 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 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 the EOC of the Sponsor (Appendix 10.1.4). 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 external unblinded statistician. Prior to final study unblinding, the external 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

cci [redacted]

CCI

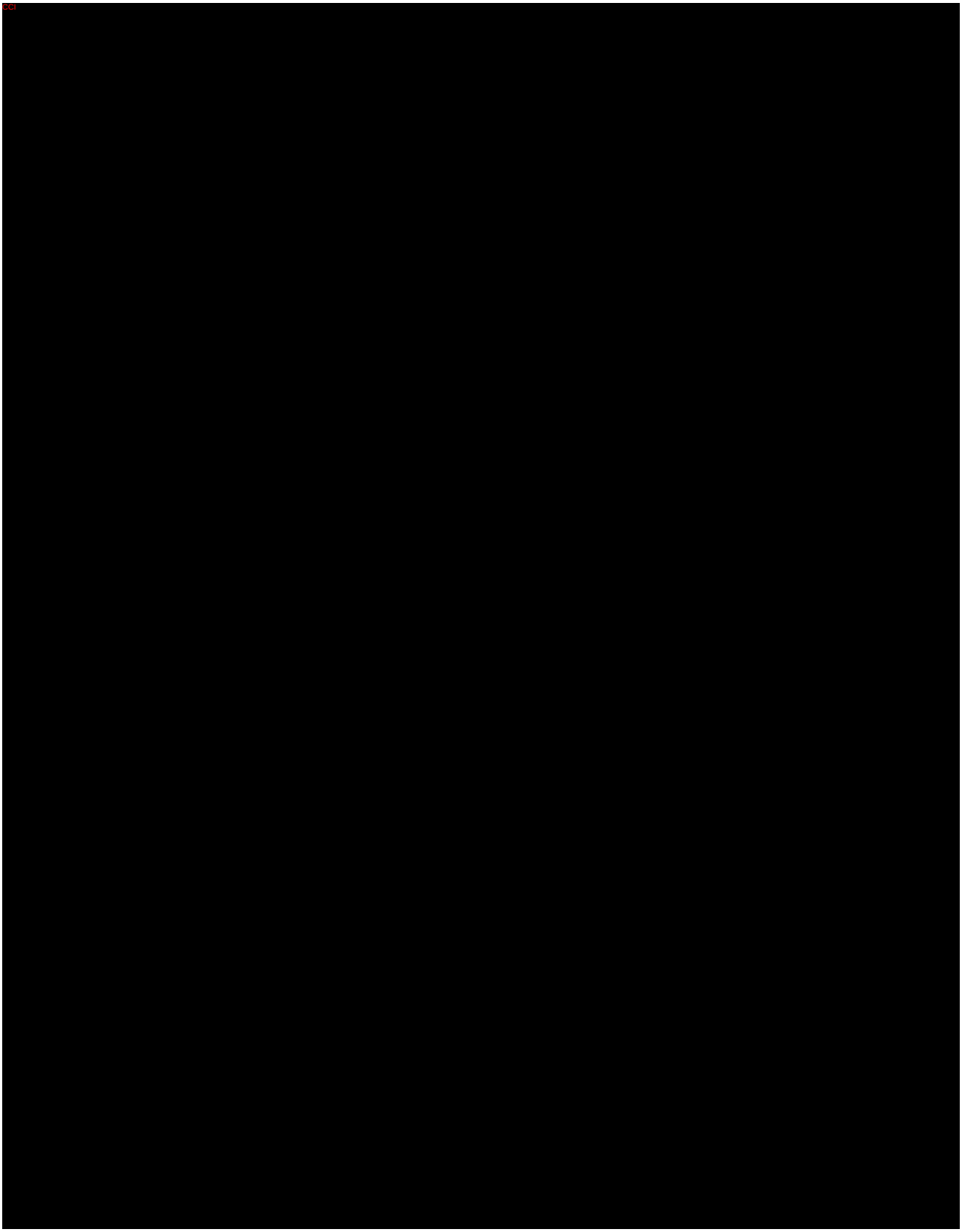
[redacted]

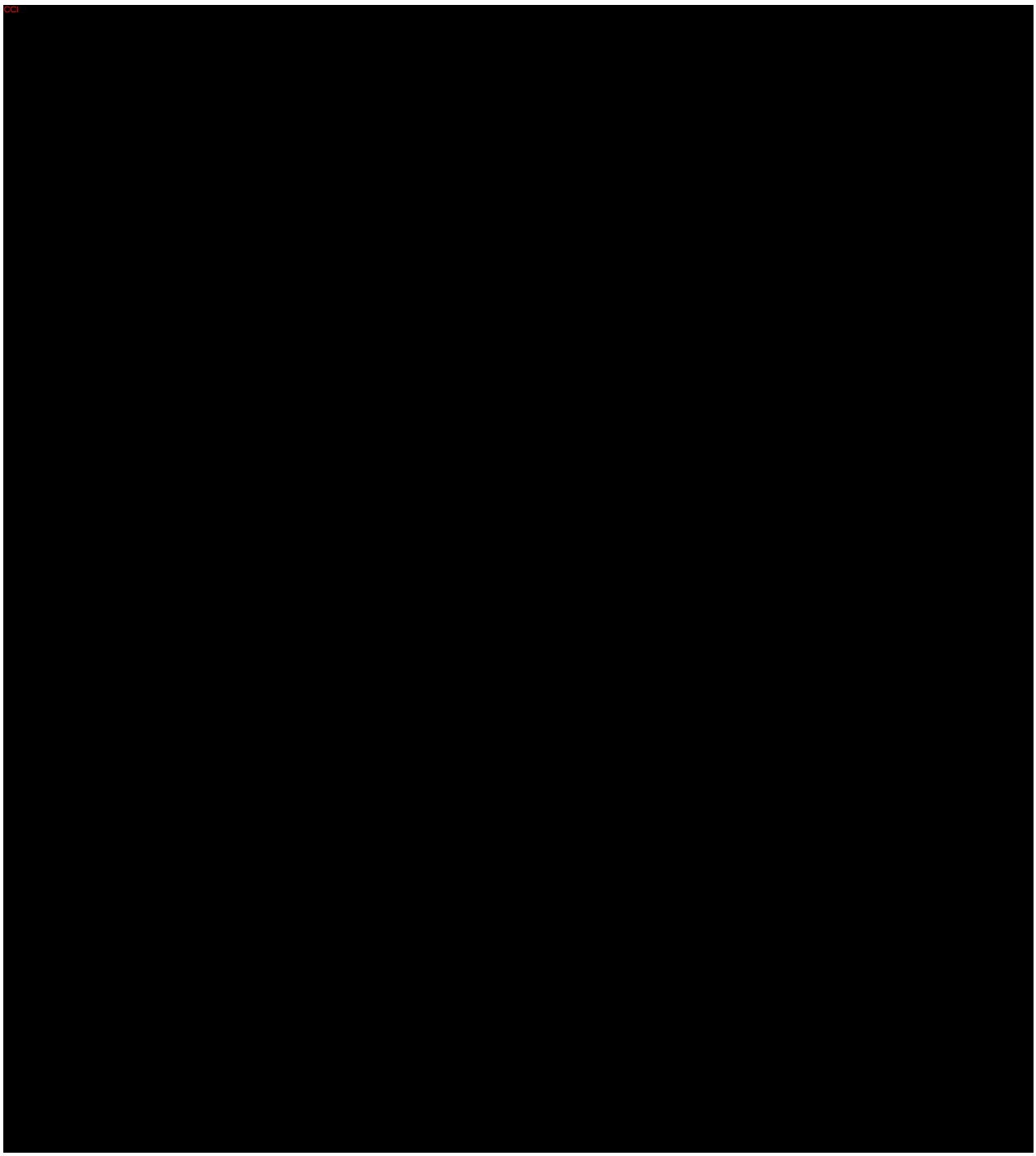
9.7.2 Safety Interim Analysis

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

CCI

[redacted]

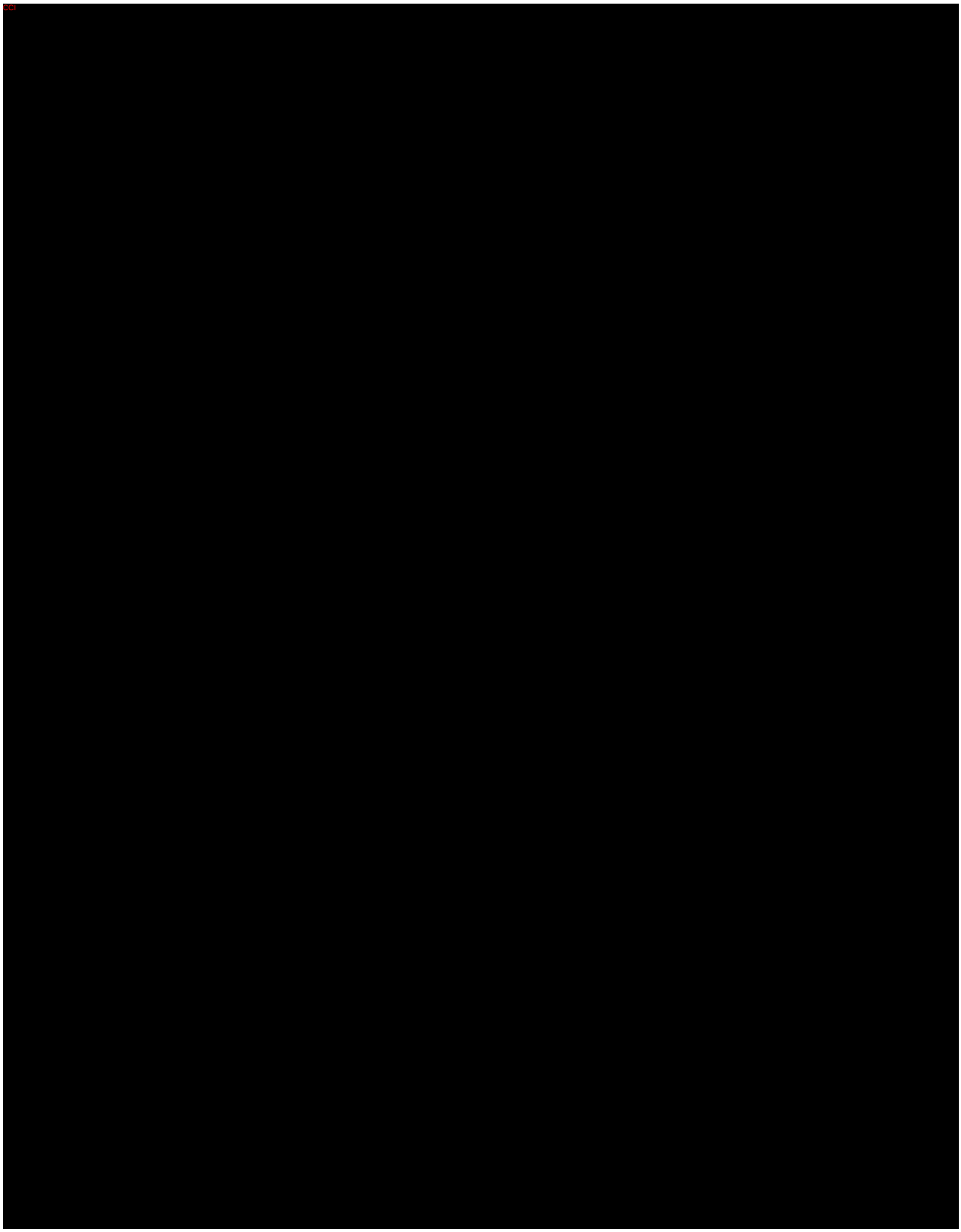


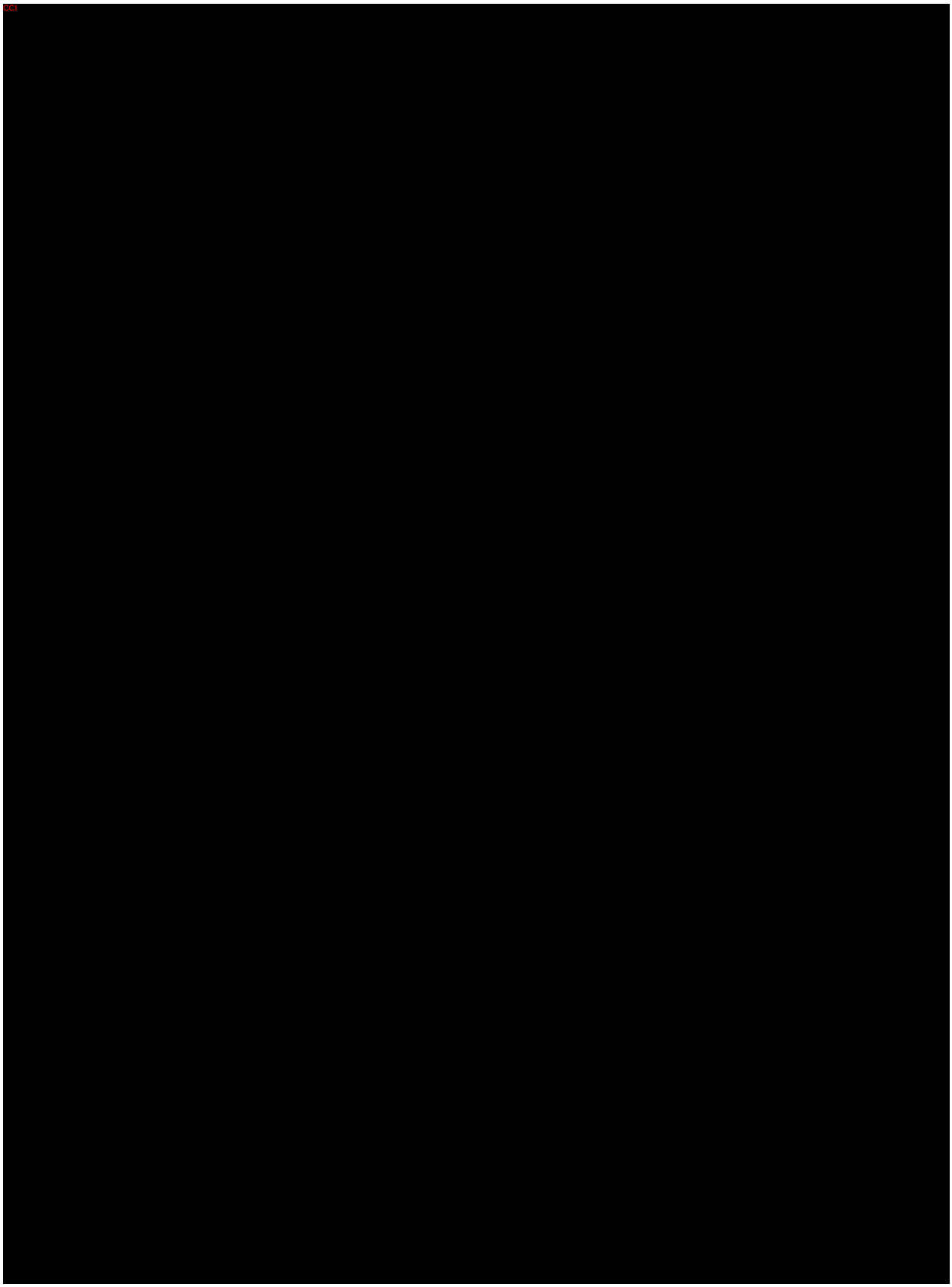


9.8.4 Safety Analyses

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 to study participants will not require a multiplicity adjustment typically associated with a planned efficacy interim analysis. 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.

combined.





CCI

[redacted]

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 versus male)
- Race: (Asian versus non-Asian)
- Stratification factors: (Section 6.3.2)
- MSI status: (MSI-H versus non MSI-H)
- ECOG status: (0 versus 1)
- Disease status (locally advanced versus metastatic)
- Primary location (stomach versus GEJ)
- Histologic subtype (diffuse versus indeterminate versus intestinal)

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in 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 (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 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 regarding the study.

10.1.4.2 External 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 (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.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarmen

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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.

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 27 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 27 Protocol-required Safety Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN[a]	Potassium	AST/SGOT	Total Bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[b]	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose	Calcium	Alkaline Phosphatase	Magnesium
	Thyroid function tests (T3 [or free T3[c]], free T4, and TSH)			
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is clinically significant)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Serum or urine pregnancy test (as needed for WOCBP). Refer to Appendix 5 • Coagulation panel (PT/INR, aPTT)[d] • Serology (HIV antibody, HBsAg, and hepatitis C virus RNA), if applicable • Tuberculosis, if applicable			

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; INR=International Normalized Ratio; PT=prothrombin time; RBC=red blood cell; RNA=ribonucleic acid; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell; WOCBP=women of childbearing potential

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 over free T3. If not available, free T3 may be tested.
d PT/INR should be tested as needed for participants on warfarin-based anticoagulation therapy.

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.

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

10.3.1 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

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

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

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

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs//worksheets.

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

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

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

    - Grade 4: Life threatening consequences; urgent intervention indicated

    - Grade 5: Death related to AE

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN

ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

10.3.5 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

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

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 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, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom cannot be used together.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception as described in Table 28 during the protocol-defined time frame in Section 5.1.

Table 28 Highly Effective Contraception Methods

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

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

1. Definitions

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

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 8.10 will be used in various experiments to understand:

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

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

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

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 protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

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 emailed 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/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Germany-specific Information:

1. Exclusion Criterion 18: HIV testing is mandatory.

2. Exclusion Criterion 19: Hepatitis B and C testing is mandatory.

3. Exclusion Criterion 20: TB testing is mandatory.

4. Sites in Germany will perform a systematic search for DPD deficiency for participants who have been naive to 5-fluorouracil or capecitabine. This research should be performed before any administration of 5-fluorouracil or capecitabine.

10.7.2 Japan-specific Information:

1. Inclusion Criterion 7: Document agreement is necessary for both the participant and their substitute if the participant is under 20 years of age.

10.7.3 UK-specific Information:

1. Exclusion Criterion 18: HIV testing is mandatory.

2. Exclusion Criterion 19: Hepatitis B and C testing is mandatory.

3. Prohibited Concomitant Medications: Live vaccines are prohibited through 3 months after the end of study intervention.

4. Pregnancy testing must be performed through 120 days after the last dose of study medication.

10.7.4 France-specific Information:

Sites in France will perform a systematic search for DPD deficiency for participants who have been naive to 5-fluorouracil or capecitabine. This research should be performed before any administration of 5-fluorouracil or capecitabine

For participants receiving oxaliplatin:

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

For participants receiving cisplatin:

- Audiometry testing must be performed every 3 months.

For participants receiving cisplatin, capecitabine, oxaliplatin and 5-fluorouracil:

- Please refer to the updated SmPC for these marketed products or the website http://base-donnees-publique.medicaments.gouv.fr, which presents the updated version of the SmPC of the medicines.

France-specific Exclusion Criteria:

30. Participants with QT/QTc interval longer than 450 msec for men and longer than 470 msec for women on the inclusion ECG.

31. Participants with clinically significant active heart disease or myocardial infarction within the last 6 months or cardiorespiratory pathology, which precludes hyperhydration for cisplatin therapy.

32. Participants receiving 5-FU or capecitabine who require treatment with phenytoin or with sorivudine or its chemically related analogs, such as brivudine.

10.7.5 Italy-specific Information:

1. Participants with significant cardiovascular impairment, including myocardial infarction, within 6 months of the first dose of study intervention should be excluded.

2. Due to clinically significant interaction between brivudine and fluoropyrimidines, recent or concomitant treatment with brivudine (or the analog sorivudine) is contraindicated. Participants on such treatment or with less than 4 weeks since last dose of brivudine (or sorivudine) should be excluded from enrollment.

3. Sites Italy will perform a systematic search for DPD deficiency for participants who have been naive to 5-fluorouracil or capecitabine. This research should be performed before any administration of 5-fluorouracil or capecitabine.

10.7.6 Czech Republic-specific Information:

1. Exclusion Criterion 18: HIV testing is mandatory.

2. Exclusion Criterion 19: Hepatitis B and C testing is mandatory.

3. Prohibited Concomitant Medications: Live vaccines are prohibited through 3 months after the end of study intervention.

4. Section 6.7 Second Course Phase: Eligibility for retreatment (termed Second Course Phase) is at the medical discretion of the site Principal Investigator provided the study remains open and the participant meets the conditions listed in Section 6.7.

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

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management (see Table 14 and Figure 2). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant 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 intervention 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 intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the iCRO for potential retrospective BICR.

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

  Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

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

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

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – 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 iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new nontarget lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

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 study, either before or after an instance of pseudo-progression.
- Nontarget lesions
    - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of 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].

10.9 Appendix 9: 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]

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
5-FU	5-fluorouracil
AE	adverse event
AHR	average hazard ratio
ALK	anaplastic lymphoma kinase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BSA	body surface area
CAPOX	capecitabine and oxaliplatin
CBC	complete blood count
CD28	cluster of differentiation 28
CD3ζ	cluster of differentiation 3 zeta
CI	confidence interval
CNS	central nervous system
CPS	combined positive score
CPS1	combined positive score ≥1
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DILI	drug-induced liver injury
DL	dose level
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation 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)
EQ-5D™	EQ-5D™ is a trademark of the EuroQoL Research Foundation
EQ-5D-5L	EuroQoL 5 Dimension Questionnaire

Abbreviation	Expanded Term
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (database)
FA	final analysis
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FISH	fluorescence in situ hybridization
FOLFOX	5-FU/oxaliplatin
FP	cisplatin and 5-fluorouracil
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
GI	gastrointestinal
H	hypothesis
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HER2/neu	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
iCRO	Imaging Contract Research Organization
IEC	Independent Ethics Committee
IFNγ	interferon gamma
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV-type	immunoglobulin-variable–type
IHC	immunohistochemistry
IL-10	interleukin 10
IND	Investigational New Drug
INR	international normalized ratio
iPR	iRECIST partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	iRECIST stable disease
ISH	in situ hybridization
iUPD	iRECIST unconfirmed progressive disease
IVD	in vitro diagnostic
ITT	Intention to Treat

Abbreviation	Expanded Term
IV	intravenous
M&N	Miettinen and Nurminen [method]
mAb	monoclonal antibody
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSD	Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI	microsatellite instability
MSI-H	microsatellite instability - high
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NR	not reached
NSAID	nonsteroidal anti-inflammatory
NSCLC	non-small cell lung carcinoma
OR	objective response
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based pharmacokinetics
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PR	partial response
PRO	patient-reported outcome(s)
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
QLG	Quality-of-Life Group
QoL	quality-of-life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOP	standard operating procedure
sSAP	supplementary Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis; Bacillus tuberculosis
TEN	Toxic Epidermal Necrolysis
T-regs	regulatory T-cells
TMDD	target-mediated drug disposition
TSH	thyroid-stimulating hormone
ULN	upper level of normal
US	United States [of America]

Abbreviation	Expanded Term
WOCBP	woman/women of childbearing potential
XP	cisplatin and capecitabine
ZAP70	zeta-chain-associated protein kinase

11 REFERENCES

[Aaronson, N. K., et al 1993]	Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.	[03Q3QL]
[Anderson, K. M. 2018]	Anderson KM, Rochoudhury S. Design and analysis of clinical trials in the presence of non-proportional hazards. Slides presented at: 2018 American Statistical Association (ASA) Biopharmaceutical Section Regulatory-Industry Statistics Workshop; 2018 Sep 12-14; Washington, DC.	[058S7S]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Cunningham, D. 2008]	Cunningham D, Oliveira J; ESMO Guidelines Working Group. Gastric cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008 May;19 Suppl 2:ii23-4.	[042LG3]
[Cunningham, D., et al 2008]	Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008 Jan 3;358(1):36-46.	[042Q5G]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]

[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[ECOG-ACRIN Cancer Research Group 2016]	ECOG-ACRIN Cancer Research Group. ECOG Performance Status [Internet]. Philadelphia: ECOG-ACRIN Cancer Research Group; 2016. Available from: http://ecog-acrin.org/resources/ecog performance-status.	[04JT28]
[Ferlay, J., et al 2014]	Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Stomach Cancer: estimated incidence, mortality and prevalence worldwide in 2012 [Internet]. Lyon: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.	[042GWS]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Fuchs, C. S., et al 2018]	Fuchs CS, Ozguroglu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, et al. Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: phase 3 KEYNOTE-061 trial [abstract]. To be presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. Abstract no. 4062.	[04X3DV]

[Fuchs, C. S., et al 2018]	Fuchs CS, Shitara K, Di Bartolomeo M, Lonardi S, Al-Batran SE, Van Cutsem E, et al. RAINFALL: a randomized, double-blind, placebo-controlled phase III study of cisplatin (Cis) plus capecitabine (Cape) or 5FU with or without ramucirumab (RAM) as first-line therapy in patients with metastatic gastric or gastroesophageal junction (G-GEJ) adenocarcinoma [abstract]. J Clin Oncol. 2018 Feb;36(4 suppl):5.	[04WXNY]
[Gandhi, L., et al 2018]	Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. In press 2018.	[04X2M4]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Maurer, W. 2013]	Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.	[03XQVB]
[Miettinen, O. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[00QHZT]

[Muro, K., et al 2016]	Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol. 2016 Jun;17(6):717-26.	[04JGHK]
[National Comprehensive Cancer Network 2013]	National Comprehensive Cancer Network. Gastric Cancer: including cancer in the proximal 5cm of the stomach, 2013.	[042MV4]
[National Comprehensive Cancer Network 2016]	National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines): gastric cancer version 2.2016 [Internet]. Washington, PA: National Comprehensive Cancer Network; 2016. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.	[04JKQ7]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Okines, A. F., et al 2009]	Okines AF, Norman AR, McCloud P, Kang YK, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol. 2009 Sep;20(9):1529-34.	[04HF4Q]

[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Pickard, A. S., et al 2007]	Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:1-8.	[00W0FM]
[Pölcher, M., et al 2010]	Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59(6):909-19.	[00VMQ8]
[Rabin, R. 2001]	Rabin, R.; de Charro, F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43.	[03QM46]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Robert, C., et al 2015]	Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun 25;372(26):2521-32.	[04G7B7]
[Ropponen, K. M., et al 1997]	Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997;182(3):318-24.	[00VMQT]
[Ryu, M. H. 2009]	Ryu MH, Kang YK. ML17032 trial: capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in advanced gastric cancer. Expert Rev Anticancer Ther. 2009 Dec;9(12):1745-51.	[042TCT]

[Schemper, M., et al 2009]	Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. Stat Med. 2009;28:2473-89.	[05N9WQ]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Shitara, K., et al 2012]	Shitara K, Ikeda J, Yokota T, Takahari D, Ura T, Muro K, et al. Progression-free survival and time to progression as surrogate markers of overall survival in patients with advanced gastric cancer: analysis of 36 randomized trials. Invest New Drugs. 2012 Jun;30(3):1224-31.	[04TDZS]
[Tabernero, J., et al 2019]	Tabernero J, Cutsem EV, Bang YJ, Fuchs CS, Wyrwicz L, Lee KW, et al. Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: the phase III KEYNOTE-062 study [abstract]. Presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; 2019 May 31-Jun 4; Chicago, IL. J Clin Oncol. 2019;37(18 suppl). Abstract no. LBA4007.	[058DD4]

[Wainberg, Z. A., et al 2017]	Wainberg ZA, Jalal SI, Muro K, Yoon HH, Garrido M, Golan T, et al. KEYNOTE-059: efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced Gastric or Gastroesophageal cancer [abstract]. Presented at European Society for Medical Oncology (ESMO); 2017 Sep 8-12; Madrid, Spain. Abstract LBA28_PR.	[04VL7L]
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]