Official Protocol Title:	A Phase III, Randomized, Double-Blind, Clinical Trial of Pembrolizumab (MK-3475) plus Chemotherapy (XP or FP) versus Placebo plus Chemotherapy (XP or FP) as Neoadjuvant/Adjuvant Treatment for Subjects with Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma (KEYNOTE-585)
NCT number:	NCT03221426
Document Date:	20-Nov-2023

Title Page

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Protocol Title: A Phase III, Randomized, Double-blind, Clinical Trial of Pembrolizumab (MK-3475) plus Chemotherapy (XP or FP) versus Placebo plus Chemotherapy (XP or FP) as Neoadjuvant/Adjuvant Treatment for Subjects with Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma (KEYNOTE-585)

Protocol Number: 585-10

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s):

IND NUMBER: 123,482

EudraCT NUMBER: 2016-004408-76

Approval Date: 20 November 2023

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 10	20-NOV-2023	The study was positive for the endpoint of pathCR based on IA1; however, based on IA3, it did not meet the prespecified criteria for statistical significance of the primary endpoint of EFS and the multiplicity strategy will not allow further statistical testing. There were no safety concerns; the study will continue to evaluate OS at the time of final analysis. Participants on treatment were unblinded to facilitate decision making.
Amendment 9	24-AUG-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 8	16-APR-2021	Promote OS to primary endpoint for the Main Study.
Amendment 7	11-JAN-2021	Amend statistical analysis plan in preparation for efficacy analyses
Amendment 6	13-DEC-2019	• The FLOT Safety Cohort will be expanded to further characterize the safety profile of the combination of FLOT with pembrolizumab and will be designated the FLOT Cohort. • Adjust the statistical analysis plan to account for an enrollment delay.
Amendment 5	14-MAR-2019	Response to Regulatory Authority input regarding safety monitoring procedures and radiation therapy.
Amendment 4	03-AUG-2018	Implement feedback from regulatory authorities and align with current pembrolizumab program standards
Amendment 3	22-MAY-2018	Introduce flexibility in electronic patient-reported outcome (ePRO) completion during the Survival Follow-up period
Amendment 2	09-JAN-2018	Include the use of the FLOT regimen as one of the options for the SOC chemotherapy backbone

Document	Date of Issue	Overall Rationale
Amendment 1	01-SEP-2017	Revise stratification information; change from central to local laboratory use
Original Protocol	25-APR-2017	Not Applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 10

Overall Rationale for the Amendment:

The study was positive for the endpoint of pathCR based on IA1; however, based on IA3, it did not meet the prespecified criteria for statistical significance of the primary endpoint of EFS and the multiplicity strategy will not allow further statistical testing. There were no safety concerns; the study will continue to evaluate OS at the time of final analysis. Participants on treatment were unblinded to facilitate decision making.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 5, Study Design	Participants on treatment were unblinded to study intervention.	This change was made to address new data. Based on IA3, the primary endpoint of EFS did not meet statistically significant superiority, although the endpoint of pathCR was positive. The multiplicity strategy will not allow further statistical testing. Participants on treatment were unblinded to facilitate decision making regarding continued treatment in the study.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 7.8, Treatment After the End of the Study	Added text indicating that participants may be enrolled into an extension study using pembrolizumab.	An extension study is available for participants to receive continued treatment and/or follow-up after completion of the study.
Section 9.1.10, Procedures for Negative Studies Without Safety Concerns	Added new subsection to describe negative studies.	To describe actions that may occur for participants when data present negative outcomes without safety concerns, and aligned with the outcome of the interim analysis in this study.
Section 9.1.11, Participant Blinding/Unblinding	Added text to describe the unblinding of participants on treatment in the China extension to make treatment decisions.	Refer to Section 5 rationale.
Section 9.3.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Added text to describe collection of safety data for participants who may enter the extension study.	To ensure reporting of safety information for participants who enter the extension study meets guidelines stated in the protocol for such reporting.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1. Synopsis

Protocol Title:

A Phase III, Randomized, Double-Blind, Clinical Trial of Pembrolizumab (MK 3475) plus Chemotherapy (XP or FP) versus Placebo plus Chemotherapy (XP or FP) as Neoadjuvant/Adjuvant Treatment for Subjects with Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma (KEYNOTE-585).

Short Title:

Phase III Trial of Pembrolizumab + Chemotherapy in Participants with Gastric or GEJ Adenocarcinoma.

Objectives/Hypotheses and Endpoints:

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

Objective/Hypothesis	Endpoint
Primary	
Main Study (XP/FP)	
• **Objective:** To evaluate event-free survival (EFS) **Hypothesis (H1):** Neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in terms of EFS based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by investigator.	• EFS based on RECIST 1.1 as assessed by investigator. EFS is defined as the time from randomization to the first of the following events: o Radiographic disease progression per RECIST 1.1 o Local or distant recurrence as assessed by CT scan or biopsy if indicated (for participants who are disease free after surgery) o Clinical progression as evidenced by peritoneal carcinomatosis confirmed by pre-operative laparoscopy or laparotomy (for participants who are confirmed to be free of peritoneal involvement by laparoscopy at screening) o Death due to any cause A second primary malignancy is not considered an EFS event. Radiographic PD during the neoadjuvant phase that does not preclude successful surgery (ie, disease free after surgery) is not considered an EFS event.

Objective/Hypothesis	Endpoint
• **Objective:** To evaluate the rate of pathological complete response based on central review. **Hypothesis (H2):** Neoadjuvant pembrolizumab plus chemotherapy is superior to neoadjuvant placebo plus chemotherapy in terms of rate of pathCR at the time of surgery. The pathCR rate is considered as an early endpoint.	• Pathological complete response (pathCR) is defined as no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes. PathCR rate is defined as the proportion of participants having pathCR.
• **Objective:** To evaluate overall survival (OS) **Hypothesis (H3):** Neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in terms of OS.	• OS is defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis will be censored at the date of last known alive.
The study is considered to have met its primary objective if neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in EFS.	
FLOT Cohort	
• **Objective:** To evaluate the safety and tolerability of pembrolizumab in combination with docetaxel, oxaliplatin, 5-FU, and leucovorin (calcium folinate) (FLOT)	• AEs • Study treatment discontinuations due to AEs

Objective/Hypothesis	Endpoint
Secondary	
Main Study (XP/FP), and Main Study (XP/FP) and FLOT Cohort Combined	
• **Objective:** To evaluate the safety and tolerability of pembrolizumab in combination with chemotherapy.	• AEs • Study treatment discontinuations due to AEs
Main Study (XP/FP)	
• **Objective:** To evaluate the disease-free survival (DFS) as assessed by investigator for participants who are disease free after surgery.	• DFS based on RECIST 1.1 as assessed by investigator. DFS is defined as the time from post-surgery baseline scan until the first occurrence of: o Local or distant recurrence o Death from any cause
Main Study (XP/FP) and FLOT Cohort Combined	
• **Objective:** To evaluate OS **Hypothesis (H4):** Neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in terms of OS.	• OS
• **Objective:** To evaluate EFS **Hypothesis (H5):** Neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in terms of EFS based on RECIST 1.1 as assessed by investigator.	• EFS based on RECIST 1.1 as assessed by investigator

Overall Design:

Study Phase	Phase III
Clinical Indication	Perioperative treatment of locally advanced resectable gastric or GEJ adenocarcinoma
Population	Adult participants with previously untreated, locally advanced resectable gastric or GEJ adenocarcinoma
Study Type	Interventional
Type of Design	Randomized, parallel-group, multi-site
Type of Control	Placebo and active control
Study Blinding	Double-blind
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 7 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 200 participants will be randomized in the FLOT Safety cohort. Approximately 800 participants will be randomized in the Main study (XP/FP). In total, approximately 1000 participants will be randomized in the entire study.

Treatment Groups and Duration:

Treatment Groups	**FLOT Cohort** A safety cohort will evaluate the combination of pembrolizumab with the chemotherapy backbone treatment known as FLOT (docetaxel + oxaliplatin + 5-FU + leucovorin [calcium folinate]). Treatment Group 1: Neoadjuvant: FLOT + pembrolizumab, followed by surgical resection. Adjuvant: FLOT + pembrolizumab followed by pembrolizumab alone. Treatment Group 2: Neoadjuvant: FLOT + placebo, followed by surgical resection. Adjuvant: FLOT + placebo followed by placebo alone. Safety analyses will be performed after participants have completed surgical resection + 30 days post-surgical evaluation. Following a review of the available safety data by the standing internal Data Monitoring Committee (siDMC), the FLOT regimen may be incorporated as one of the standard-of-care chemotherapy backbones in the main study. As of Amendment 06, the FLOT Safety Cohort will be expanded to 200 participants and will be designated the FLOT Cohort. Future interim analyses of the FLOT Cohort will be monitored by the external DMC. **Main Study (XP/FP)** Treatment Group 1: Neoadjuvant: [cisplatin + capecitabine (XP) or cisplatin + 5-fluorouracil (FP)] + pembrolizumab, followed by surgical resection. Adjuvant: [XP or FP] + pembrolizumab followed by pembrolizumab alone. Treatment Group 2: Neoadjuvant: [XP or FP] + placebo, followed by surgical resection. Adjuvant: [XP or FP] + placebo followed by placebo alone. The investigator will decide the chemotherapy backbone (XP or FP) prior to randomization. Participants will continue on the chemotherapy chosen prior to randomization throughout the study and will not be allowed to switch between chemotherapy treatments (exception may be granted after Sponsor consultation, eg, participants who have difficulty swallowing oral study treatment).

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, each eligible participant will be randomized into 1 of the 2 treatment groups. The participant will receive 3 cycles of neoadjuvant and 14 cycles of adjuvant treatment with study medication. Each participant assigned will receive study treatment until one of the conditions for discontinuation of study treatment is met. All participants will be followed for EFS and OS. After the end of treatment, participants will have a 30-day assessment for AE monitoring (serious adverse events will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anti-cancer therapy, whichever occurs first). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. Participants who discontinue treatment for reasons other than disease progression/recurrence will have post-treatment follow-up scans for disease status until any of the conditions for discontinuation of scans are met. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study.

Study governance considerations are outlined in Appendix 1. A list of abbreviations used in this document can be found in Appendix 8.

2. Schedule of Activities (SoA)

2.1 FLOT Cohort

2.1.1 Neoadjuvant Combination Treatment Group 1: FLOT + Pembrolizumab OR Neoadjuvant Combination Treatment Group 2: FLOT + Placebo

Study Period:	**Screening Phase**				**Treatment Cycles**						**Notes**
Treatment Cycles:					**C1 D1**	**C1 D15**	**C2 D1**	**C2 D8**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
Admin Procedures											
Informed Consent	X										Written consent must be obtained prior to performing any protocol-specified procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management is acceptable in lieu of a screening test if performed within the specified time frame. Screening number will be assigned when the study informed consent is signed.
Informed Consent for Future Biomedical Research	X										Providing FBR sample(s) is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Appendix 2. The FBR consent does not need to be signed during the screening period; it may be signed during the study.
Inclusion/Exclusion Criteria		X									See Sections 6.1 and 6.2.
Participant Identification Card	X										See Section 9.1.3.
Demographics and Medical History		X									See Section 9.1.4.

Study Period:	**Screening Phase**				**Treatment Cycles**						**Notes**
Treatment Cycles:					**C1 D1**	**C1 D15**	**C2 D1**	**C2 D8**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X		Prior medications – Record all medications taken within 30 days of first dose. Concomitant medications – enter new medications started during the study through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Appendix 4.
Pembrolizumab 200 mg or placebo					X		X		X		See Sections 7.1 and 9.1.8.1.
FLOT											
Docetaxel 50 mg/m^2					X	X		X	X		See Sections 7.1 and 9.1.8.1.
Oxaliplatin 85 mg/m^2					X	X		X	X		
5-FU 2600 mg/m^2					X	X		X	X		
Leucovorin (calcium folinate) 200 mg/m^2					X	X		X	X		
Efficacy Procedures											
Tumor Imaging		X							X		Area to be imaged: chest, abdomen, and pelvis. The first on-study scan will be performed after completion of 3 cycles of preoperative therapy. See Section 9.2.1.
Tumor Staging		X									Tumor staging prior to enrollment must consist of at least 1 imaging modality: CT or MRI (ie, not limited to laparoscopic staging or endoscopic ultrasound). Follow the current edition of the American Joint Committee on Cancer (AJCC) staging guidelines. Lauren histological classification required at baseline.
Surgery										X	See Section 9.2.2.
pathCR Assessment										X	See Section 9.2.2.1.

Study Period:	**Screening Phase**				**Treatment Cycles**						**Notes**
Treatment Cycles:					**C1 D1**	**C1 D15**	**C2 D1**	**C2 D8**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
ePROs (HRQoL Measures)					X				X		Perform within 3 days prior to Day 1 of the cycles indicated. It is strongly recommended that ePROs are administered prior to administration of study medication, AE evaluation, and disease status notification. See Section 9.2.4.
Safety Procedures											
Review AEs	X	X	X	X	X	X	X	X	X	X*	See Section 9.3. *AEs must be assessed during the surgical period however this is not a clinic visit.
Full Physical Examination			X								See Section 9.5.1.1. Height will be measured at Visit 1 only.
Directed Physical Examination					X	(X)[b]	X	(X)[b]	X		Perform within 3 days prior to administration of study treatment on the days and cycles indicated. See Section 9.5.1.2.
Vital Signs and Weight			X		X	(X)[b]	X	(X)[b]	X		During the treatment period, perform within 3 days prior to administration of study treatment on the days and cycles indicated. See Section 9.5.2.
12-Lead ECG (Local)			X								See Section 9.5.3.
ECOG Performance Status				X	X	(X)[b]	X	(X)[b]	X		ECOG status must be performed **within 3 days** of beginning of Cycle 1 and prior to each treatment administration. See Section 9.5.4.
Pregnancy Test – Serum or Urine				X	X	(X)[b]	X	(X)[b]	X		For women of reproductive potential, perform during the treatment period within 72 hours prior to administration of study treatment on the days and cycles indicated, and perform 30 days post-treatment discontinuation. See Section 9.5.6.

Study Period:	**Screening Phase**				**Treatment Cycles**						**Notes**
Treatment Cycles:					**C1 D1**	**C1 D15**	**C2 D1**	**C2 D8**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
PT/INR and aPTT/PTT				X							All laboratory tests will be performed by a local laboratory. During the treatment period, perform within 72 hours prior to administration of study treatment on the days and cycles indicated. See Section 9.5.5.
CBC with Differential				X		(X)[b]	X	(X)[b]	X		
Chemistry Panel				X		(X)[b]	X	(X)[b]	X		
Urinalysis				X							
T3 or Free T3, FT4, and TSH				X			X				During the treatment period, perform within 21 days prior to study drug administration on Day 1 of Cycle 2. See Section 9.5.5.
Biomarkers/FBR											
Blood for Genetic Analysis					X						Perform within 72 hours prior to administration of study treatment on the days and cycles indicated. See Sections 9.8 and 9.9.
Blood for RNA Analyses					X		X		X		
Blood for Serum Biomarker Analyses					X		X		X		
Blood for ctDNA					X				X		
Archived or Newly Obtained Tissue Collection for Biomarker Testing	X										Tumor tissue for biomarker analysis is required at baseline. Tumor tissue may be from newly obtained core biopsy, excisional biopsy, biopsy by endoscopy (FNA is not adequate) or archival tissue sample (where available). Archival tissue sample (FFPE block), may be collected up to 1 year before treatment start and submitted during the screening period. Consent must be obtained prior to tumor tissue submission/collection. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. See Sections 9.8 and 9.9.

Study Period:	**Screening Phase**				**Treatment Cycles**						**Notes**
Treatment Cycles:					**C1 D1**	**C1 D15**	**C2 D1**	**C2 D8**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
Newly Obtained Tissue Collection for Biomarker Testing										X	Representative samples from relevant sections of the tumor tissue obtained during the surgery are required for biomarker analysis and pathCR.

Admin=administrative; AE=adverse event; aPTT=activated partial thromboplastin time; C=Cycle; CBC=complete blood count; ctDNA=circulating tumor deoxyribonucleic acid; CT=computed tomography; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ePROs=electronic patient-reported outcomes; FBR=future biomedical research; FLOT=docetaxel + oxaliplatin + 5-FU + leucovorin (calcium folinate); FNA=fine needle aspirate; FT4=free thyroxine; 5-FU=5-fluorouracil; FP=cisplatin +5-FU; HRQoL=Health Related Quality of Life; INR=international normalized ratio; MRI=magnetic resonance imaging; pathCR=pathological complete response; PT=prothrombin time; PTT=partial thromboplastin time; RNA=ribonucleic acid; T3=triiodothyronine; TSH=thyroid stimulating hormone; XP=cisplatin + capecitabine.

[a] Unless otherwise specified, the window for each visit is ±3 days. Cycle 1 study treatment must begin as close to treatment allocation as possible and must be given within 3 days of allocation.
[b] C1D15 and C2D8 assessments are only required for participants receiving FLOT.

2.1.2 Adjuvant Combination Treatment Group 1: FLOT + Pembrolizumab OR Adjuvant Combination Treatment Group 2: FLOT + Placebo

Study Period:	**Treatment Cycles[a]**					**Notes**
Treatment Cycles:	**C1 D1**	**C1 D15**	**C2 D1**	**C2 D8**	**C3 D1**	
Scheduling Window (Days)[b]:	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	
Admin Procedures						
Prior and Concomitant Medication Review	X	X	X	X	X	Concomitant medications – Enter new medications started during the study through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Appendix 4.
Pembrolizumab 200 mg or placebo	X		X		X	See Sections 7.1 and 9.1.8.1.
FLOT						
Docetaxel 50 mg/m^2	X	X		X	X	See Sections 7.1 and 9.1.8.1.
Oxaliplatin 85 mg/m^2	X	X		X	X	
5-FU 2600 mg/m^2	X	X		X	X	
Leucovorin (calcium folinate) 200 mg/m^2	X	X		X	X	
Efficacy Procedures						
Tumor Imaging	X					See Section 9.2.1.
ePROs (HRQoL Measures)	X				X	Perform within 3 days prior to Day 1 of the cycles indicated. It is strongly recommended that ePROs are administered prior to administration of study medication, AE evaluation, and disease status notification. See Section 9.2.4.
Safety Procedures						
Review AEs	X	X	X	X	X	See Section 9.3.
Directed Physical Examination	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on the days and cycles indicated. See Section 9.5.1.2.

Study Period:	**Treatment Cycles[a]**					**Notes**
Treatment Cycles:	**C1 D1**	**C1 D15**	**C2 D1**	**C2 D8**	**C3 D1**	
Scheduling Window (Days)[b]:	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	
Vital Signs and Weight	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on the days and cycles indicated. See Section 9.5.2.
ECOG Performance Status	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on the days and cycles indicated. See Section 9.5.4.
Pregnancy Test – Serum or Urine	X	X	X	X	X	For women of reproductive potential, perform within 72 hours prior to administration of study treatment on the days and cycles indicated, and perform 30 days post-treatment discontinuation. See Section 9.5.6.2.
CBC with Differential	X	X	X	X	X	All laboratory tests will be performed by a local laboratory. Perform within 72 hours prior to administration of study treatment on the days and cycles indicated. See Section 9.5.5.
Chemistry Panel	X	X	X	X	X	
T3 or Free T3, FT4, and TSH			X			Perform within 21 days prior to study drug administration on Day 1 of Cycle 2. See Section 9.5.5.
Biomarkers/FBR						
Blood for RNA Analyses	X					Perform within 72 hours prior to administration of study treatment on Day 1 of Cycle 1. See Sections 9.8 and 9.9.
Blood for Serum Biomarker Analyses	X					
Blood for ctDNA	X					

Admin=administrative; AE=adverse event; C=Cycle; CBC=complete blood count; ctDNA=circulating tumor deoxyribonucleic acid; D=Day; ECOG=Eastern Cooperative Oncology Group; ePROs=electronic patient-reported outcomes; FBR=future biomedical research; FT4=free thyroxine; 5-FU=5-fluorouracil; FLOT=docetaxel + oxaliplatin + 5-FU + leucovorin (calcium folinate); HRQoL=Health Related Quality of Life; IV=intravenous; PD=progressive disease; RNA=ribonucleic acid; T3=triiodothyronine; TSH=thyroid stimulating hormone.

[a.] Adjuvant combination therapy should be started 4 to 10 weeks post-surgery.
[b.] Unless otherwise specified, the window for each visit is ± 3 days.

2.1.3 Adjuvant Monotherapy Treatment Group 1: Pembrolizumab OR Adjuvant Monotherapy Treatment Group 2: Placebo

Study Period:	**Treatment Cycles**											**Notes**
Treatment Cycles:	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**	**C8 D1**	**C9 D1**	**C10 D1**	**C11 D1**	**C12 D1**	**C13 D1**	**C14[b] D1**	
Scheduling Window (Days)[a]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Admin Procedures												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	Concomitant medications – Enter new medications started during the study through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Appendix 4.
Pembrolizumab 200 mg or placebo	X	X	X	X	X	X	X	X	X	X	X	See Sections 7.1 and 9.1.8.1.
Efficacy Procedures												
Tumor Imaging		X				X				X		See Section 9.2.1.
ePROs (HRQoL Measures)	X			X			X				X	Perform within 3 days prior to Day 1 of the cycles indicated. It is strongly recommended that ePROs are administered prior to administration of study medication, AE evaluation, and disease status notification. See Section 9.2.4.
Safety Procedures												
Review AEs	X	X	X	X	X	X	X	X	X	X	X	See Section 9.3.
Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.1.2.
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.2.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1of each cycle. See Section 9.5.4.
Pregnancy Test – Serum or Urine	X	X	X	X	X	X	X	X	X	X	X	For women of reproductive potential, perform within 72 hours prior to administration of study treatment on Day 1of each cycle, and perform 30 days post-treatment discontinuation. See Section 9.5.6.

Study Period:	**Treatment Cycles**											**Notes**
Treatment Cycles:	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**	**C8 D1**	**C9 D1**	**C10 D1**	**C11 D1**	**C12 D1**	**C13 D1**	**C14[b] D1**	
Scheduling Window (Days)[a]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
CBC with Differential		X		X		X		X		X	X	All laboratory tests will be performed by a local laboratory. Perform within 72 hours prior to administration of study treatment on Day 1 of the cycles indicated. See Section 9.5.5.
Chemistry Panel		X		X		X		X		X	X	
T3 or Free T3, FT4, and TSH		X		X		X		X		X	X	Perform within 21 days prior administration of study treatment on Day 1 of the cycles indicated. See Section 9.5.5.

Admin=administrative; AE=adverse event; CBC=complete blood count; ECOG=Eastern Cooperative Oncology Group; ePROs=electronic patient-reported outcomes; FT4=free thyroxine; HRQoL=Health Related Quality of Life; IV=intravenous; PD=progressive disease; T3=triiodothyronine; TSH=thyroid stimulating hormone.

[a.] Unless otherwise specified, the window for each visit is ± 3 days.
[b.] Participants completing all 14 cycles of adjuvant treatment will not have an end of treatment visit and their next visit will be the safety follow-up visit.

2.1.4 End of Treatment and Post-treatment Study Period

Study Period:	**End of Treatment**	**Post-treatment Follow-up**			**Notes**
		Safety Follow-up	**Efficacy Follow-up[a]**	**Survival Follow-up[b]**	
Timepoints:	**At Time of Treatment Discontinuation**	**30 Days after last dose of treatment**	**Every 12 Weeks**	**Every 12 Weeks**	
Scheduling Window (Days)	**± 3**	**± 3**	**± 7**	**± 7**	
Admin Procedures					
Prior and Concomitant Medication Review	X	X			Concomitant medications – Enter new medications started during the study through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Appendix 4.
Post-study Anti-cancer Therapy Status		X	X	X	
Survival Status[b]	←----------	----------	----------	X	See Section 9.10.4.
Efficacy Procedures					
Tumor Imaging	X		X		See Section 9.2.1.3.
ePROs (HRQoL Measures)	X		X	X	See Section 9.2.4.
Safety Procedures					
Review AEs	X	X	X		See Section 9.3. Record all AEs occurring within 30 days after the last dose of study treatment. Report all SAEs (related and unrelated to study treatment) occurring up until 90 days after the last dose of study treatment or 30 days after the end of treatment if the participant initiates new anti-cancer therapy, whichever occurs first. Afterwards, report only SAEs that are related to study treatment.
Full Physical Examination	X				See Section 9.5.1.1.
Vital Signs and Weight					See Section 9.5.2.
ECOG Performance Status	X				See Section 9.5.4.
Pregnancy Test – Serum or Urine		X			For women of reproductive potential, perform 30 days post-treatment discontinuation. See Section 9.5.6.

Study Period:	**End of Treatment**	**Post-treatment Follow-up**			**Notes**
		Safety Follow-up	**Efficacy Follow-up[a]**	**Survival Follow-up[b]**	
Timepoints:	**At Time of Treatment Discontinuation**	**30 Days after last dose of treatment**	**Every 12 Weeks**	**Every 12 Weeks**	
Scheduling Window (Days)	**± 3**	**± 3**	**± 7**	**± 7**	
CBC with Differential	X	X			See Section 9.5.5. Labs do not need to be repeated after the end of treatment if labs are within normal range.
Chemistry Panel	X	X			
T3 or Free T3, FT4, and TSH		X			
Biomarkers/FBR					
Blood for RNA Analyses	X				See Sections 9.8 and 9.9.
Blood for Serum Biomarker Analyses	X				
Blood for ctDNA	X				
Newly Obtained Tissue Collection	X (optional if recurrence)				An optional newly obtained core or excisional biopsy (FNA not adequate) can be collected at treatment discontinuation if tumor has recurred. This biopsy is requested but not required. Endoscopic biopsies are permitted. See Sections 9.8 and 9.9.

Admin=administrative; AE=adverse event; CBC=complete blood count; ctDNA=circulating tumor deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; ePROs=electronic patient-reported outcomes; FBR=future biomedical research; FNA=fine needle aspirate; FT4=free thyroxine; HRQoL=Health Related Quality of Life; PD=progressive disease; RNA=ribonucleic acid; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

[a] The Efficacy Follow-up visits should be scheduled to coincide with the scan schedule the participant is on at the time of treatment discontinuation.
[b] After the start of new anti-cancer treatment or documented PD, the participant should be contacted by telephone approximately every 12 weeks to assess for survival status. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

2.2 Main Study (XP/FP)

2.2.1 Neoadjuvant Combination Phase (3 cycles)

2.2.1.1 Neoadjuvant Combination Treatment Group 1: XP or FP + Pembrolizumab OR Neoadjuvant Combination Treatment Group 2: XP or FP + Placebo

Study Period:	**Screening Phase**				**Treatment Cycles**				**Notes**
Treatment Cycles:					**C1 D1**	**C2 D1**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
Admin Procedures									
Informed Consent	X								Written consent must be obtained prior to performing any protocol-specified procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management is acceptable in lieu of a screening test if performed within the specified time frame. Screening number will be assigned when the study informed consent is signed.
Informed Consent for Future Biomedical Research	X								Providing FBR sample(s) is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Appendix 2. The FBR consent does not need to be signed during the screening period; it may be signed during the study.
Inclusion/Exclusion Criteria		X							See Sections 6.1 and 6.2.
Participant Identification Card	X								See Section 9.1.3.
Demographics and Medical History		X							See Section 9.1.4.
Prior and Concomitant Medication Review	X	X	X	X	X	X	X		Prior medications – Record all medications taken within 30 days of first dose. Concomitant medications – Enter new medications started during the study through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Appendix 4.

Study Period:	**Screening Phase**				**Treatment Cycles**				**Notes**
Treatment Cycles:					**C1 D1**	**C2 D1**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
Pembrolizumab 200 mg or placebo					X	X	X		See Sections 7.1 and 9.1.8.1.
XP/FP									
Cisplatin 80 mg/m2					X	X	X		See Sections 7.1 and 9.1.8.1.
Capecitabine 1000 mg/m^2 or 5-FU 800 mg/m^2/day					X	X	X		See Sections 7.1 and 9.1.8.1.
Efficacy Procedures									
Tumor Imaging		X					X		Area to be imaged: chest, abdomen, and pelvis. The first on-study scan will be performed after completion of 3 cycles of preoperative therapy. See Section 9.2.1.
Tumor Staging		X							Tumor staging prior to enrollment must consist of at least 1 imaging modality: CT or MRI (ie, not limited to laparoscopic staging or endoscopic ultrasound). Follow the current edition of the American Joint Committee on Cancer (AJCC) staging guidelines. Lauren histological classification required at baseline.
Surgery								X	See Section 9.2.2.
pathCR Assessment								X	See Section 9.2.2.1.
ePROs (HRQoL Measures)					X		X		Perform within 3 days prior to Day 1 of the cycles indicated. It is strongly recommended that ePROs are administered prior to administration of study medication, AE evaluation, and disease status notification. See Section 9.2.4.
Safety Procedures									
Review AEs	X	X	X	X	X	X	X	X*	See Section 9.3. *AEs must be assessed during the surgical period, however this is not a clinic visit.
Full Physical Examination			X						See Section 9.5.1.1. Height will be measured at Visit 1 only.
Directed Physical Examination					X	X	X		Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.1.2.

Study Period:	**Screening Phase**				**Treatment Cycles**				**Notes**
Treatment Cycles:					**C1 D1**	**C2 D1**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
Vital Signs and Weight			X		X	X	X		Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.2.
12-Lead ECG (Local)			X						See Section 9.5.3.
ECOG Performance Status				X	X	X	X		ECOG status must be performed **within 3 days** of beginning of Cycle 1 and prior to each treatment administration. See Section 9.5.4.
Pregnancy Test – Serum or Urine				X	X	X	X		For women of reproductive potential, during the treatment period, perform within 72 hours prior to administration of study treatment on Day 1 of each cycle, and perform 30 days post-treatment discontinuation. See Section 9.5.6.
PT/INR and aPTT/PTT				X					All laboratory tests will be performed by a local laboratory. During the treatment period, laboratory tests are performed within 72 hours prior to administration of study treatment on Day 1 of the cycles indicated. See Section 9.5.5.
CBC with Differential				X		X	X		
Chemistry Panel				X		X	X		
Urinalysis				X					
T3 or Free T3, FT4, and TSH				X		X			During the treatment period, perform within 21 days prior to study drug administration on Day 1 of Cycle 2. See Section 9.5.5.
Biomarkers/FBR									
Blood for Genetic Analysis					X				Perform within 72 hours prior to administration of study treatment on the days and cycles indicated. See Sections 9.8 and 9.9.
Blood for RNA Analyses					X	X	X		
Blood for Serum Biomarker Analyses					X	X	X		
Blood for ctDNA					X		X		

Study Period:	**Screening Phase**				**Treatment Cycles**				**Notes**
Treatment Cycles:					**C1 D1**	**C2 D1**	**C3 D1**	**Surgery**	
Scheduling Window (Days)[a]:	**-42 to -1**	**-28 to -1**	**-21 to -1**	**-10 to -1**		**± 3**	**± 3**	**3 to 9 weeks after C3D1**	
Archived or Newly Obtained Tissue Collection for Biomarker Testing	X								Tumor tissue for biomarker analysis is required at baseline. Tumor tissue may be from newly obtained core biopsy, excisional biopsy, biopsy by endoscopy (FNA is not adequate) or archival tissue sample (where available). Archival tissue sample (FFPE block), may be collected up to 1 year before treatment start and submitted during the screening period. Consent must be obtained prior to tumor tissue submission/collection. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. See Sections 9.8 and 9.9.
Newly Obtained Tissue Collection for Biomarker Testing								X	Representative samples from relevant sections of the tumor tissue obtained during the surgery are required for biomarker analysis and pathCR.

Admin=administrative; AE=adverse event; aPTT=activated partial thromboplastin time; CBC=complete blood count; ctDNA=circulating tumor deoxyribonucleic acid; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ePROs=electronic patient-reported outcomes; FBR=future biomedical research; FNA=fine needle aspirate; FP=cisplatin + 5-FU; FT4=free thyroxine; 5-FU=5-fluorouracil; HRQoL=Health Related Quality of Life; INR=international normalized ratio; MRI=magnetic resonance imaging; pathCR=pathological complete response; PT=prothrombin time; PTT=partial thromboplastin time; RNA=ribonucleic acid; T3=triiodothyronine; TSH=thyroid stimulating hormone; XP=cisplatin + capecitabine.

[a.] Unless otherwise specified, the window for each visit is ±3 days. Cycle 1 study treatment must begin as close to treatment allocation as possible and must be given within 3 days of allocation.

2.2.2 Adjuvant Combination Phase (3 cycles)

2.2.2.1 Adjuvant Combination Treatment Group 1: XP or FP + Pembrolizumab OR Adjuvant Combination Treatment Group 2: XP or FP + Placebo

Study Period:	**Treatment Cycles[a]**			**Notes**
Treatment Cycles:	**C1 D1**	**C2 D1**	**C3 D1**	
Scheduling Window (Days)[b]:	**± 3**	**± 3**	**± 3**	
Admin Procedures				
Prior and Concomitant Medication Review	X	X	X	Concomitant medications – Enter new medications started during the study through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Appendix 4.
Pembrolizumab 200 mg or placebo	X	X	X	See Sections 7.1 and 9.1.8.1.
XP/FP				
Cisplatin 80 mg/m^2	X	X	X	See Sections 7.1 and 9.1.8.1.
Capecitabine 1000 mg/m^2 or 5-FU 800 mg/m^2/day	X	X	X	See Sections 7.1 and 9.1.8.1.
Efficacy Procedures				
Tumor Imaging	X			See Section 9.2.1.
ePROs (HRQoL Measures)	X		X	Perform within 3 days prior to Day 1 of the cycles indicated. It is strongly recommended that ePROs are administered prior to administration of study medication, AE evaluation, and disease status notification. See Section 9.2.4.
Safety Procedures				
Review AEs	X	X	X	See Section 9.3.
Directed Physical Examination	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.1.2.
Vital Signs and Weight	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.2.

Study Period:	**Treatment Cycles[a]**			**Notes**
Treatment Cycles:	**C1 D1**	**C2 D1**	**C3 D1**	
Scheduling Window (Days)[b]:	**± 3**	**± 3**	**± 3**	
ECOG Performance Status	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.4.
Pregnancy Test – Serum or Urine	X	X	X	For women of reproductive potential, perform within 72 hours prior to administration of study treatment on Day 1 of each cycle, and perform 30 days post-treatment discontinuation. See Section 9.5.6.
CBC with Differential	X	X	X	All laboratory tests will be performed by a local laboratory. Perform within 72 hours prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.5.
Chemistry Panel	X	X	X	
T3 or Free T3, FT4, and TSH		X		Perform within 21 days prior to administration of study treatment on Day 1 of Cycle 2. See Section 9.5.5.
Biomarkers/FBR				
Blood for RNA Analyses	X			Perform within 3 days prior to administration of study treatment on Day 1 of Cycle 1. See Sections 9.8 and 9.9.
Blood for Serum Biomarker Analyses	X			
Blood for ctDNA	X			

Admin=administrative; AE=adverse event; C=Cycle; CBC=complete blood count; ctDNA=circulating tumor deoxyribonucleic acid; D=Day; ECOG=Eastern Cooperative Oncology Group; ePROs=electronic patient-reported outcomes; FBR=future biomedical research; FP=cisplatin + 5-fluorouracil; FT4=free thyroxine; 5-FU=5-fluorouracil; HRQoL=Health Related Quality of Life; IV=intravenous; PD=progressive disease; RNA=ribonucleic acid; T3=triiodothyronine; TSH=thyroid stimulating hormone; XP=cisplatin + capecitabine.

[a.] Adjuvant combination therapy should be started 4-10 weeks post-surgery.

[b.] Unless otherwise specified, the window for each visit is ± 3 days.

2.2.3 Adjuvant Monotherapy Phase (11 Cycles)

2.2.3.1 Adjuvant Monotherapy Treatment Group 1: Pembrolizumab or Adjuvant Monotherapy Treatment Group 2: Placebo

Study Period:	**Treatment Cycles**											**Notes**
Treatment Cycles:	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**	**C8 D1**	**C9 D1**	**C10 D1**	**C11 D1**	**C12 D1**	**C13 D1**	**C14[b] D1**	
Scheduling Window (Days)[a]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Admin Procedures												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	Concomitant medications – Enter new medications started during the study through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Appendix 4.
Pembrolizumab 200 mg or placebo	X	X	X	X	X	X	X	X	X	X	X	See Sections 7.1 and 9.1.8.1.
Efficacy Procedures												
Tumor Imaging		X				X				X		See Section 9.2.1.
ePROs (HRQoL Measures)	X			X			X				X	Perform within 3 days prior to Day 1 of the cycles indicated. It is strongly recommended that ePROs are administered prior to administration of study medication, AE evaluation, and disease status notification. See Section 9.2.4.
Safety Procedures												
Review AEs	X	X	X	X	X	X	X	X	X	X	X	See Section 9.3.
Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.1.2.
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.2.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	Perform within 3 days prior to administration of study treatment on Day 1 of each cycle. See Section 9.5.4.
Pregnancy Test – Serum or Urine	X	X	X	X	X	X	X	X	X	X	X	For women of reproductive potential, perform within 72 hours prior to administration of study treatment on Day 1 of each cycle, and perform 30 days post-treatment discontinuation. See Section 9.5.6.

Study Period:	**Treatment Cycles**											**Notes**
Treatment Cycles:	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**	**C8 D1**	**C9 D1**	**C10 D1**	**C11 D1**	**C12 D1**	**C13 D1**	**C14[b] D1**	
Scheduling Window (Days)[a]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
CBC with Differential		X		X		X		X		X	X	All laboratory tests will be performed by a local laboratory. Perform within 72 hours prior to administration of study treatment on Day 1 of the cycles indicated. See Section 9.5.5.
Chemistry Panel		X		X		X		X		X	X	
T3 or Free T3, FT4, and TSH		X		X		X		X		X	X	Perform within 21 days prior to administration of study treatment on Day 1 of the cycles indicated. See Section 9.5.5.

Admin=administrative; AE=adverse event; C=Cycle; CBC=complete blood count; D=Day; ECOG=Eastern Cooperative Oncology Group; ePROs=electronic patient-reported outcomes; FT4=free thyroxine; HRQoL=Health Related Quality of Life; IV=intravenous; PD=progressive disease; T3=triiodothyronine; TSH=thyroid stimulating hormone.

[a.] Unless otherwise specified, the window for each visit is ± 3 days.
[b.] Participants completing all 14 cycles of adjuvant treatment will not have an end of treatment visit and their next visit will be the safety follow-up visit.

2.2.4 End of Treatment and Post-treatment Study Period

Study Period:	**End of Treatment**	**Post-Treatment Follow-Up**			**Notes**
		Safety Follow-up	**Follow-up Visits[a]**	**Survival Follow-up[b]**	
Timepoints:	**At Time of Treatment Discontinuation**	**30 Days After Last Dose of Treatment**	**Every 12 Weeks**	**Every 12 Weeks**	
Scheduling Window (Days):	**± 3**	**± 3**	**± 7**	**± 7**	
Admin Procedures					
Prior and Concomitant Medication Review	X	X			Concomitant medications – Enter new medications started during the study through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Appendix 4.
Post-study Anti-cancer Therapy Status		X	X	X	
Survival Status[b]	←----------	----------	----------	---------→ X	See Section 9.10.4.
Efficacy Procedures					
Tumor Imaging	X		X		See Section 9.2.1.3.
ePROs (HRQoL Measures)	X		X	X	See Section 9.2.4.
Safety Procedures					
Review AEs	X	X	X		See Section 9.3. Record all AEs occurring within 30 days after the last dose of study treatment. Report all SAEs (related and unrelated to study treatment) occurring up until 90 days after the last dose of study treatment or 30 days after the end of treatment if the participant initiates new anti-cancer therapy, whichever occurs first. Afterwards, report only SAEs that are related to study treatment.
Full Physical Examination	X				See Section 9.5.1.1.
Vital Signs and Weight					See Section 9.5.2.
ECOG Performance Status	X				See Section 9.5.4.
Pregnancy Test – Serum or Urine		X			For women of reproductive potential, perform 30 days post-treatment discontinuation. See Section 9.5.6.

Study Period:	**End of Treatment**	**Post-Treatment Follow-Up**			**Notes**
		Safety Follow-up	**Follow-up Visits[a]**	**Survival Follow-up[b]**	
Timepoints:	**At Time of Treatment Discontinuation**	**30 Days After Last Dose of Treatment**	**Every 12 Weeks**	**Every 12 Weeks**	
Scheduling Window (Days):	**± 3**	**± 3**	**± 7**	**± 7**	
CBC with Differential	X	X			See Section 9.5.5. Labs do not need to be repeated after the end of treatment if labs are within normal range.
Chemistry Panel	X	X			
T3 or Free T3, FT4, and TSH		X			
Biomarkers/FBR					
Blood for RNA Analyses	X				See Sections 9.8 and 9.9.
Blood for Serum Biomarker Analyses	X				
Blood for ctDNA	X				
Newly Obtained Tissue Collection	X (optional if recurrence)				An optional newly obtained core or excisional biopsy (FNA not adequate) can be collected at treatment discontinuation if tumor has recurred. This biopsy is requested but not required. Endoscopic biopsies are permitted. See Sections 9.8 and 9.9.

Admin=administrative; AE=adverse event; CBC=complete blood count; ctDNA=circulating tumor deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; ePROs=electronic patient-reported outcomes; FBR=future biomedical research; FNA=fine needle aspirate; FT4=free thyroxine; HRQoL=Health Related Quality of Life; PD=progressive disease; RNA=ribonucleic acid; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

[a] The Follow-up visits should be scheduled to coincide with the scan schedule the participant is on at the time of treatment discontinuation.
[b] After the start of new anti-cancer treatment or documented PD, the participant should be contacted by telephone approximately every 12 weeks to assess for survival status. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study, whichever occurs first.

3. Introduction

3.1 Study Rationale

3.1.1 Rationale for the Study and Selected Participant Population

Cancers of the upper gastrointestinal (GI) tract are a group of highly aggressive malignancies and a major public health problem globally. Approximately 951,600 new cases of gastric cancer are diagnosed annually. These cancers are responsible for 723,100 annual deaths worldwide [Torre, L. A., et al 2015]. In the United States alone, 28,000 new cases of stomach cancer are estimated to be diagnosed in 2017, with approximately 10,960 deaths attributed to this disease. Despite the evolution in the management of locoregional disease with multimodality treatment strategies, gastric cancer continues to remain as one of the most lethal malignancies with 5-year survival rates reaching only 22% [Siegel, R. L., et al 2017]. These results are far too short of our goal to achieve a cure for these patients, particularly for those diagnosed with non-metastatic disease.

There is no uniformly accepted standard of practice for the management of these patients at this time. Therefore, a wide range of treatment approaches are encountered in clinical practice depending on the institution, geographical region, and personal preferences of the treating oncologist. It is an urgent unmet need to identify effective novel strategies for the treatment of these patients that are aimed at improving the clinical outcomes beyond the activity of the existing approaches. Targeting the immune checkpoint pathways to activate the host immune system against cancer cells is one such novel approach that is rapidly evolving in the recent years.

3.1.1.1 Rationale for Neoadjuvant Treatment

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study (ISRCTN 93793971), sponsored by the United Kingdom Medical Research Council, provided evidence that perioperative chemotherapy confers longer overall survival (OS) to participants with gastric or gastroesophageal cancer [Cunningham, D., et al 2006]. The study included approximately 500 participants from the United Kingdom, Netherlands, Germany, Brazil, Singapore, and New Zealand who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and were diagnosed with potentially resectable gastric, gastroesophageal junction (GEJ), or distal esophageal cancer with a grade of T2 or higher; 74% of participants enrolled had gastric tumors, 15% had GEJ tumors, and 11% had distal esophageal tumors. Participants were randomized to receive surgery alone or surgery along with both neoadjuvant and adjuvant chemotherapy. Chemotherapy consisted of 3 cycles each of preoperative and postoperative treatment consisting of every 3-week infusions of epirubicin, cisplatin, and continuous fluorouracil. Participants receiving radical surgery and chemotherapy had a higher rate of curative resection (79%) than participants receiving radical surgery alone (70%; p=0.03) as assessed by the surgeons. Importantly, participants receiving chemotherapy also had significantly higher 5-year survival rates (36%) compared with patients receiving surgery only (23%). This study provided the first evidence from a large randomized controlled study that perioperative chemotherapy improves OS in this population.

The Fédération Francophone de Cancérologie Digestive (FFCD) 9703 study was a multi-center randomized controlled study performed in France [Ychou, M., et al 2011]. The study enrolled 224 participants with gastric, GEJ, or distal esophageal cancer judged to be amenable to curative resection, and performance status of ECOG 0 or 1. Most of the participants (64%) had GEJ tumors, while smaller numbers had gastric (25%) or esophageal (11%) tumors. Participants were randomized to receive surgery alone or surgery plus neoadjuvant chemotherapy (2 or 3 cycles of cisplatin + 5-fluorouracil [FP]); the protocol recommended that participants receiving neoadjuvant therapy also receive FP adjuvant therapy, though only about half of the participants in that group received adjuvant therapy. Overall, participants receiving perioperative chemotherapy had a higher curative (R0) resection rate compared with participants receiving surgery only (84% versus 73%, p=0.04), with no evident difference in postoperative complications. Participants receiving chemotherapy also had a higher 5-year OS rate (38% versus 24%).

Together with results from the MAGIC study, the results from the FFCD study show that perioperative chemotherapy can improve the rate of potentially curative resection and extend OS of patients in this population.

3.1.1.2 Rationale for Adjuvant Treatment

Postoperative adjuvant chemotherapy in gastric cancer is primarily supported by the Adjuvant Chemotherapy Trial of TS1 for Gastric Cancer (ACTS-GC) [Sasako, M., et al 2011] and the Capecitabine and Oxaliplatin Adjuvant Trial in Stomach Cancer (CLASSIC) [Bang, Y. J., et al 2012] studies, both of which investigated the role of chemotherapy after gastrectomy with D2 dissection. The Japanese ACTS-GC study randomly assigned 1,059 participants with Stage II or III gastric cancer to surgery alone or surgery followed by 1 year of S-1 (an orally bioavailable prodrug of fluorouracil) chemotherapy. S-1–treated participants had a 5-year OS of 71.7% versus 61.1% for those who received surgery alone (hazard ratio [HR], 0.67; 95% confidence interval (CI), 0.54 to 0.83). The Asian CLASSIC study randomly assigned 1,035 participants with Stage II or III gastric cancer after curative D2 gastrectomy to treatment with 6 months of capecitabine plus oxaliplatin or surgery alone. The results online at www.clinicaltrials.gov (Identifier NCT02339324) demonstrated an improved 3-year disease-free survival (DFS) in the chemotherapy group compared with surgery alone (74% versus 59%; HR, 0.56; 95% CI, 0.44 to 0.72).

Two recent meta-analyses including studies from around the world support the use of adjuvant postoperative chemotherapy for patients and demonstrate a 15% to 18% decreased risk of death with the addition of chemotherapy postoperatively [GASTRIC Group, et al 2010] [Diaz-Nieto, R., et al 2013].

3.1.1.3 Clinical Studies With Pembrolizumab in Gastric Cancer

The KEYNOTE 012 study [Muro, K., et al 2014] is a Phase IB, multi-cohort study of participants with recurrent or metastatic gastric or GEJ adenocarcinoma who expressed programmed cell death-ligand 1 (PD-L1) (≥1% by immunohistochemistry). This cohort enrolled 39 participants (19 from Asia and 20 outside of Asia). The primary endpoint was overall response rate (ORR). Although 69% of participants received 2 or more prior lines of

chemotherapy, pembrolizumab monotherapy demonstrated an ORR of 20.5% by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) per central radiology assessment (95% CI: 9.3%, 36.5%; 7 partial responses [PRs], 1 complete response [CR]), and was similar in participants from Asia and outside of Asia. Responses were observed across all lines of treatment. Forty-four percent of the participants with measurable disease displayed some degree of tumor shrinkage from baseline. As of the data cutoff date of 26-Apr-2016, the median duration of response was 9.5 months. The 6-month PFS and OS were 24% and 67%, respectively, in this heavily pretreated group. Based on these data, there appears to be a correlation between response and degree of PD-L1 positivity.

Single-agent pembrolizumab at a dose and frequency of 10 mg/kg every 2 weeks [Q2W] was generally well tolerated, with the type, severity, and frequency of adverse events (AEs) similar to that observed in other indications.

The overall safety results of pembrolizumab in participants treated with single agent pembrolizumab at a dose and frequency of 10 mg/kg Q2W with gastric cancer reported in this study were consistent with the previously established pembrolizumab safety profile based on data in melanoma, non-small cell lung cancer (NSCLC), and head and neck cancer (see the Investigator's Brochure (IB) for information about AEs in other indications). There were 3 deaths reported in the gastric cancer cohort, with none of these fatal serious adverse events (SAEs) attributed to study treatment.

The KEYNOTE 028 is a Phase Ib, non-randomized, multi-cohort study that treated 23 participants with PD-L1 positive esophageal cancer; 17 with squamous cell cancer and 5 with adenocarcinoma [Semrad, T. J. 2015]. Seven out of 23 participants (30%) had PR and of the 5 participants with adenocarcinoma, 2 participants had PR and 2 participants had stable disease.

KEYNOTE 059 is a Phase II, non-randomized, multi-site, open-label study of pembrolizumab in participants with gastric or GEJ adenocarcinoma. A total of 315 participants were enrolled across 3 cohorts to examine the safety and efficacy of pembrolizumab. Cohort 1 participants who had progressed on at least 2 prior systemic treatments for advanced disease (third-line [3L]+participants) that received pembrolizumab as monotherapy; (Cohort 2) participants who had not previously received systemic therapy for advanced disease (first-line [1L] participants) received pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU). Sites in Japan also administered pembrolizumab in combination with cisplatin and capecitabine; and (Cohort 3) PD-L1-positive participants who had not previously received systemic therapy for advanced disease (1L participants) who received pembrolizumab as monotherapy. The primary objectives of the study were to determine the safety, tolerability, and ORR of pembrolizumab (200 mg fixed dose every 3 weeks [Q3W]) given as first and third-line monotherapy to participants with gastric or GEJ adenocarcinoma whose tumors expressed PD-L1, and to determine the safety and tolerability of pembrolizumab administered in combination with cisplatin and 5-FU as first-line therapy in participants with gastric or GEJ adenocarcinoma. The primary endpoint was overall response rate (ORR). As of the data cutoff date of 16-Jan-2017:

In Cohort 1 (3L+ participants receiving pembrolizumab monotherapy), ORR (CR + PR) was 11.6%, of which 2.3% (6 participants) had a CR, and 42.4% of participants experienced a reduction in measurable tumor size. The median PFS was 2.0 months. The PFS rates at 3 and 6 months were 29.0% and 14.1%, respectively. The median OS was 5.6 months. The OS rates were 46.5% and 23.4% at 6 and 12 months, respectively. As of the data cutoff date, 87 participants continued to survive beyond 8 months with 27 participants surviving longer than 12 months.

In Cohort 2 (1L participants receiving pembrolizumab in combination with cisplatin + 5-FU or capecitabine), ORR was 60.0%. Of the responders, 1 participant (4.0%) had a CR. The median PFS was 6.6 months. The PFS rates at 3 and 6 months were 88.0% and 68.0%, respectively. The median OS was 20.8 months. The OS rates were 76.0% and 54.9% at 6 and 12 months, respectively.

In Cohort 3 (1L participants receiving pembrolizumab monotherapy), ORR was 25.8%. Of the responders, 1 participant (3.2%) had a CR. The median PFS was 3.3 months. The PFS rates at 3 and 6 months were 51.6% and 34.9%, respectively. The median OS was not reached as of the data cutoff date. The OS rates were 72.6% and 61.7% at 6 months and 12 months, respectively.

The safety results from KEYNOTE 059 were generally consistent with the established safety profile of pembrolizumab in the target populations. This study also established the safety and efficacy of pembrolizumab in combination with cisplatin and fluoropyrimidine-based chemotherapy in patients with gastric and GEJ adenocarcinoma.

KEYNOTE 061 is a randomized, multi-center, open-label study of pembrolizumab versus paclitaxel as 2L treatment in participants with advanced gastric or GEJ adenocarcinoma who had progressed after failure of any combination chemotherapy containing a platinum and a fluoropyrimidine agent. Enrollment in this study has completed and 592 participants were randomized. The enrollment included all participants without regard for PD-L1 expression status. The overall study enrollment was driven by the number of participants with PD-L1 positive expression on their tumor (n=360). That is, enrollment was stopped when approximately 360 participants with PD-L1 positive expression on their tumor had been randomized. Additionally, there was a cap on enrollment (30% of the total) for participants residing in the Asia-Pacific region for this study. The primary efficacy endpoints are PFS and OS. The study is currently ongoing and following participants for OS.

KEYNOTE 062 is a Phase III randomized, active-controlled, multi-site, partially blinded, study of pembrolizumab, or pembrolizumab + cisplatin + 5-FU versus placebo + cisplatin + 5-FU, as first-line treatment in PD-L1 positive, human epidermal growth factor receptor 2 negative participants with advanced gastric or GEJ adenocarcinoma. The study has completed enrollment and approximately 750 participants have been randomized in a 1:1:1 ratio among the 3 treatment groups, to compare the efficacy and safety of pembrolizumab or pembrolizumab + cisplatin +5-FU versus placebo + cisplatin + 5-FU as a first-line treatment. Participants were, stratified by geographic region, disease status, and fluoropyrimidine treatment. The study has dual primary endpoints of OS and progression-free survival (PFS), and patients will be monitored for safety every 6 months.

KEYNOTE 063 is a Phase III, randomized, multi-center, open-label study of pembrolizumab versus paclitaxel in Asian participants with advanced gastric or GEJ adenocarcinoma who have progressed after failure of any combination chemotherapy containing a platinum and a fluoropyrimidine agent. This planned study will enroll approximately 360 PD-L1 positive participants (approximately 70% to 80% of the total will be from China). The primary efficacy endpoints are PFS and OS.

3.1.1.4 Clinical Studies With Neoadjuvant Pembrolizumab

In addition, neoadjuvant pembrolizumab with or without chemotherapy is currently being studied in multiple solid tumors, including:

- Phase Ib/II Study of Neoadjuvant Pembrolizumab With Gemcitabine-Cisplatin (Cisplatin-Eligible) or Gemcitabine (Cisplatin-Ineligible) in Subjects With T2-4aN0M0 Urothelial Cancer: HCRN GU14-188 (study start May 2015, end March 2018; available at www.clinicaltrials.gov: NCT02365766)

- Neoadjuvant Pembrolizumab for Unresectable Stage III and Unresectable Stage IV Melanoma (study start January 2015; end February 2017; available at www.clinicaltrials.gov: NCT02306850)

- A Clinical Trial to Evaluate the Effect of Neoadjuvant MK-3475 (Pembrolizumab) Therapy on Intratumoral Immune Infiltrates in Renal Cell Cancer (RCC) Patients Undergoing Surgical Resection (study start December 2014, end February 2016; available at www.clinicaltrials.gov: NCT02212730)

- Immunotherapy With MK-3475 in Locoregionally Advanced, Surgically Resectable Head and Neck Squamous Cell Carcinoma (study start March 2015, end March 2022; available at www.clinicaltrials.gov: NCT02296684)

- Neoadjuvant Combination Biotherapy with Pembrolizumab (MK-3475) and High Dose IFN-α2b in Patients with Locally/Regionally Advanced/Recurrent Melanoma: Safety, Efficacy and Biomarker Study (study start December 2014; available at www.clinicaltrials.gov: NCT02339324)

- A Randomized Multicenter Phase Ib/II study to assess the safety and the immunological effect of chemoradiation therapy (CRT) in combination with Pembrolizumab (MK-3475) compared to CRT alone in patients with resectable or borderline resectable pancreatic cancer (study start March 2015, end 2019; available at www.clinicaltrials.gov: NCT02305186)

3.2 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent

receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications including patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (Combined Positive Score (CPS) ≥1) as determined by an FDA-approved test, with disease progression on or after ≥2 prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy. For more details on specific indications refer to the IB.

3.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation 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 [Dong, H., et al 2002] [Sharpe, A. H. and Freeman, G. J. 2002] [Brown, J. A., et al 2003] [Francisco, L. M., et al 2010] [Thompson, R. H., et al 2007]. In particular, the presence of cluster of differentiation CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells correlates with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Talmadge, J. E., et al 2007] [Usubütün, A., et al 1998].

The structure of murine PD-1 has been resolved [Al-Shibli, K. I., et al 2008]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2 to the ITSM 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 [Talmadge, J. E., et al 2007] [Deschoolmeester, V., et al 2010] [Diez, M., et al 1998] [Galon, J., et al 2006].

The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from, that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [Hiraoka, N. 2010] [Nobili, C., et al 2008]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and natural killer cells [Hodi, F. S. and Dranoff, G. 2010] [Kloor, M. 2009]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of

macrophages and dendritic cells [Hillen, F., et al 2008]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [Lee, H. E., et al 2008] [Leffers, N., et al 2009] [Nishimura, H., et al 2000] [Hiraoka, N. 2010]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [Hiraoka, N. 2010]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in participants with melanoma [Liotta, F., et al 2011].

In gastric cancer, PD-L1 and PD-L2 overexpression have recently been associated with Epstein-Barr virus-positive tumors [Cancer Genome Atlas Research Network 2014]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and can be an attractive target for therapeutic intervention.

3.2.2 Pre-clinical and Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor 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 the presence of interferon gamma (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]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

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

3.2.3 Ongoing Clinical Studies of Pembrolizumab in Malignancies

Ongoing clinical studies are being conducted in advanced melanoma, NSCLC, a number of advanced solid tumor indications including gastric and GEJ adenocarcinomas (detailed in Section 3.1.1.3), and hematologic malignancies. For study details, please refer to the IB.

3.3 Benefit/Risk Assessment

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

Beneficial effects of pembrolizumab have been seen in several studies to date. Publications of a significantly positive benefit:risk ratio have been reported for melanoma in a single arm study encompassing nearly 1,000 participants (KEYNOTE 001), which led to FDA approval in September 2014, and in a randomized comparison to chemotherapy (KEYNOTE 002 is further detailed in the IB). Additional potential benefits are addressed in Section 3.1.1.3, which details responses of the KEYNOTE 012 study; a multi-cohort Phase Ib study of which one cohort enrolled participants with recurrent or metastatic gastric or GEJ adenocarcinoma that expressed PD-L1 (≥1% by immunohistochemistry). Although two-thirds of participants received at least 2 prior therapies for advanced disease, pembrolizumab monotherapy achieved an ORR of 20.5% by RECIST v.1.1 central radiology assessment (95% CI [9.3%, 36.5%]; 7 partial responses, 1 complete response). The median duration of response was 9.5 months (range 5.6 to 22.1 months).

In KEYNOTE 012, the most common AEs included abdominal pain (35.9%), decreased appetite (30.8%), fatigue (30.8%), nausea (28.2%), and vomiting (25.6%). Fatigue (10.3%) was the only Grade 3 to 5 AE that was reported in >10% of participants. There were 12.8% of participants who experienced drug-related Grade 3 to 4 AEs. There were no drug-related Grade 5 (fatal) AEs reported.

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

4. Objectives/Hypotheses and Endpoints

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

Objective/Hypothesis	Endpoint
Primary	
Main Study (XP/FP)	
• **Objective:** To evaluate event-free survival (EFS) **Hypothesis (H1):** Neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab, is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in terms of EFS based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by investigator.	• EFS based on RECIST 1.1 as assessed by investigator. EFS is defined as the time from randomization to the first of the following events: o Radiographic disease progression per RECIST 1.1 o Local or distant recurrence as assessed by CT scan or biopsy if indicated (for participants who are disease free after surgery) o Clinical progression as evidenced by peritoneal carcinomatosis confirmed by pre-operative laparoscopy or laparotomy (for participants who are confirmed to be free of peritoneal involvement by laparoscopy at screening) o Death due to any cause A second primary malignancy is not considered an EFS event. Radiographic PD during the neoadjuvant phase that does not preclude successful surgery (i.e., disease free after surgery) is not considered an EFS event.
• **Objective:** To evaluate the rate of pathological complete response based on central review. **Hypothesis (H2):** Neoadjuvant pembrolizumab plus chemotherapy is superior to neoadjuvant placebo plus chemotherapy in terms of rate of pathCR at the time of surgery. The pathCR rate is considered an early endpoint.	• Pathological complete response (pathCR) is defined as no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes. PathCR rate is defined as the proportion of participants having pathCR.

Objective/Hypothesis	Endpoint
• **Objective:** To evaluate overall survival (OS) **Hypothesis (H3):** Neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in terms of OS.	• OS is defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis will be censored at the date of last known alive.
The study is considered to have met its primary objective if neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in EFS.	
FLOT Cohort	
• Objective: To evaluate the safety and tolerability of pembrolizumab in combination with docetaxel, oxaliplatin, 5-FU, and leucovorin (calcium folinate) (FLOT).	• AEs • Study treatment discontinuations due to AEs
Secondary	
Main Study (XP/FP), and Main Study (XP/FP) and FLOT Cohort Combined	
• **Objective**: To evaluate the safety and tolerability of pembrolizumab in combination with chemotherapy.	• AEs • Study treatment discontinuations due to AEs
Main Study (XP/FP)	
• **Objective**: To evaluate the disease-free survival (DFS) as assessed by investigator for participants who are disease free after surgery.	• DFS based on RECIST 1.1 as assessed by investigator. DFS is defined as the time from post-surgery baseline scan until the first occurrence of: o Local or distant recurrence o Death from any cause

Objective/Hypothesis	Endpoint
Main Study (XP/FP) and FLOT Cohort Combined	
• **Objective:** To evaluate OS **Hypothesis (H4):** Neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in terms of OS.	• OS
• **Objective:** To evaluate EFS **Hypothesis (H5):** Neoadjuvant and adjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab is superior to neoadjuvant and adjuvant placebo plus chemotherapy, followed by adjuvant placebo in terms of EFS based on RECIST 1.1 as assessed by investigator.	• EFS based on RECIST 1.1 as assessed by investigator
Tertiary/Exploratory	
Main Study (XP/FP) and FLOT Cohort Combined	
• **Objective:** To evaluate the rate of pathological complete response based on central review.	• PathCR rate
• **Objective**: To evaluate the DFS as assessed by investigator for participants who are disease free after surgery.	• DFS based on RECIST 1.1 as assessed by investigator
Main Study (XP/FP), and Main Study (XP/FP) and FLOT Cohort Combined	
• **Objective:** To evaluate efficacy by participant's programmed cell death ligand 1 (PD-L1) status.	• OS, EFS, pathCR rate as appropriate
• **Objective:** To evaluate the R0 resection rate	• R0 resection rate

Objective/Hypothesis	Endpoint
• **Objective:** To evaluate changes in health-related quality of life (HRQoL) assessments from baseline in neoadjuvant and adjuvant phases using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC Gastric Cancer–Specific Quality of Life Questionnaire (EORTC QLQ-STO22).	• EORTC QLQ-C30 and EORTC QLQ-STO22 change from baseline
• **Objective:** To characterize utilities in participants with gastric cancer in neoadjuvant and adjuvant phases using EuroQoL-5 Dimension Questionnaire (EQ-5D-5L).	• EQ-5D-5L
• **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 in combination with chemotherapy and other treatments.	• Biomarker analyses may include germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry, and other blood-derived biomarkers.

5. Study Design

NOTE: Based on IA3, there was a trend towards improvement in EFS; however, the study was not able to show statistically significant superiority of EFS in the main cohort of pembrolizumab plus chemotherapy compared to placebo plus chemotherapy. The study was positive for the endpoint of pathCR based on IA1. No new safety concerns were identified. After review of these results by the external DMC, the recommendation was to continue the study to final analysis; no additional statistical testing is possible per the multiplicity strategy of the statistical plan (see Sections 10.2, 10.7, and 10.8). Refer to Section 9.1.10 for details regarding negative studies without safety concerns.

Participants on treatment after IA3 was conducted have been unblinded to study intervention to facilitate shared decision-making between the investigator and participant regarding continued treatment in the study. The investigator may consider continuing study intervention for a participant, in consultation with the Sponsor, if the participant is benefitting from the study intervention and it is in the participant's best interest to continue.

If study intervention is continued, administration will follow the description in Section 7.1 and all protocol-specified procedures will be performed as in the SoA (see Section 2).

Participants discontinuing study intervention, should complete a Discontinuation Visit. A Safety Follow-up Visit will be performed 30 days after treatment discontinuation. All remaining study procedures will be performed as described in the SoA (Section 2), including Efficacy and Survival follow-up. Reporting of safety information will occur as described in Section 9.3.3 and Section 9.3.4.

Participants may be eligible to enroll in an extension study as described in Section 7.8.

5.1 Overall Design

This is a Phase III, randomized, placebo-controlled, multi-site, double-blinded study in participants diagnosed with previously untreated, locally advanced resectable gastric or GEJ adenocarcinoma. In the main study, participants will be randomized to receive pembrolizumab (Treatment Group 1) or placebo (Treatment Group 2), administered in addition to the standard of care chemotherapy backbone treatments XP or FP. Concurrently, a FLOT Safety Cohort will be opened at selected sites to evaluate the safety of the FLOT regimen and pembrolizumab. The FLOT regimen will only be added as an additional chemotherapy backbone in the main study if the data from the FLOT Safety Cohort establishes safety of the regimen in combination with pembrolizumab. As of Amendment 06, the FLOT Safety Cohort will be expanded to enroll 200 participants and will be designated the FLOT Cohort. 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.

5.1.1 Main Study (XP/FP)

Approximately 800 participants will be randomized in a 1:1 ratio to receive pembrolizumab (Treatment Group 1) or placebo (Treatment Group 2), administered in addition to standard of care chemotherapy backbone treatments (Table 1). The protocol is open to enrollment and sites may enroll participants in the study and choose either the XP or FP chemotherapy backbone.

Table 1 Main Study: Treatment Dose and Schedule

Neoadjuvant Combination Phase (3 cycles) and Adjuvant Combination Phase (3 cycles)
Group 1: XP or FP + pembrolizumab 200 mg
Group 2: XP or FP + placebo
Adjuvant Monotherapy Phase (11 cycles)
Group 1: pembrolizumab 200 mg
Group 2: placebo

Abbreviations: FP=cisplatin + 5-FU; XP=cisplatin + capecitabine.

1 treatment cycle=3 weeks duration (treatment cycles are based on pembrolizumab/placebo administration)

Pembrolizumab or placebo: administered on Day 1 of each treatment cycle every 3 weeks (Q3W).

Standard of Care Chemotherapy backbones:

- XP: cisplatin (80 mg/m^2 administered on Day 1 of each treatment cycle, Q3W) + capecitabine (1000 mg/m^2 administered 2 times a day from Day 1 to Day 14 of each treatment cycle, Q3W), for 3 cycles in the neoadjuvant phase and 3 cycles in the adjuvant phase
- FP: cisplatin (80 mg/m^2 administered on Day 1 of each treatment cycle, Q3W) + 5-FU (800 mg/m^2/day administered from Day 1 to Day 5 of each treatment cycle Q3W), for 3 cycles in the neoadjuvant phase and 3 cycles in the adjuvant phase

The investigator will decide the chemotherapy backbone (XP or FP) prior to randomization. Participants will continue on the chemotherapy chosen prior to randomization throughout the study and will not be allowed to switch between chemotherapy treatments (exception may be granted after Sponsor consultation eg, participants who have difficulty swallowing oral study treatment).

Schedule of Assessments

Regardless of chemotherapy regimen, study treatment must begin on the day of randomization or within 3 days of allocation/randomization.

Neoadjuvant study treatment will be administered pre-operatively for 3 cycles.

After neoadjuvant (pre-operative) treatment, all participants will have a scan prior to surgery and will be re-evaluated for surgical resectability. If there is no evidence of metastatic disease, and the tumor is assessed to be surgically resectable, the participants will undergo a potentially curative surgical resection within 3 to 9 weeks after Cycle 3 Day 1 of pre-operative treatment.

Participants who undergo surgery and have a complete surgical resection (R0 resection) will continue to receive the planned post-operative therapy as specified in the protocol adjuvant treatment plan. Participants will have a post-surgery baseline scan that must be completed within 2 weeks prior to starting the first dose of the adjuvant treatment.

Adjuvant study treatment will start within 4 to 10 weeks after surgery and will consist of a total of 14 cycles (3 cycles of combination phase treatment, followed by 11 cycles of monotherapy phase treatment).

Participants with microscopic evidence of disease at surgical margins (R1) or macroscopic residual disease (R2) following surgical resection may continue protocol planned adjuvant treatment if the planned treatment for the participant is perioperative chemotherapy and resection. Alternatively, the participants will be permitted to have radiation therapy (RT) based on published standards in this disease, in addition to the protocol planned adjuvant treatment after surgery.

Participants will be followed by scans every 12 weeks (±7 days) from the post-surgery baseline scan. Two years (24 months) after the date of the post-surgery baseline scan, the scan schedule will be reduced to every 24 weeks (±7 days). Participants will be followed until disease progression/recurrence.

Participants who are not able to undergo surgery may continue protocol-planned adjuvant treatment as prolonged neoadjuvant therapy or palliative therapy or will be permitted to have radiation therapy (in addition to the protocol planned treatment) if such therapy is the planned medical treatment for the participant. The next cycle of treatment may begin after 21 days ±3 days) from the last cycle of neo-adjuvant therapy, or per local guidelines. These participants will be followed by scans every 12 weeks (±7 days) from the post-neoadjuvant scan. The schedule will be reduced to every 24 weeks (±7 days), 2 years after the post-neoadjuvant scan.

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

The primary and secondary objectives of the study are described in Section 4.

Details about interim analyses are in Section 10.7. An independent, external DMC will monitor the safety and efficacy of this study.

This study will be conducted in conformance with Good Clinical Practices (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 have 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) and details pertaining to the statistical analyses for participants enrolled in China will be provided in a separate sSAP.

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

NOTE: Country-specific protocol operational items are described in Appendix 9.

5.1.1.1 Main Study Diagram

The main study design is depicted in Figure 1.

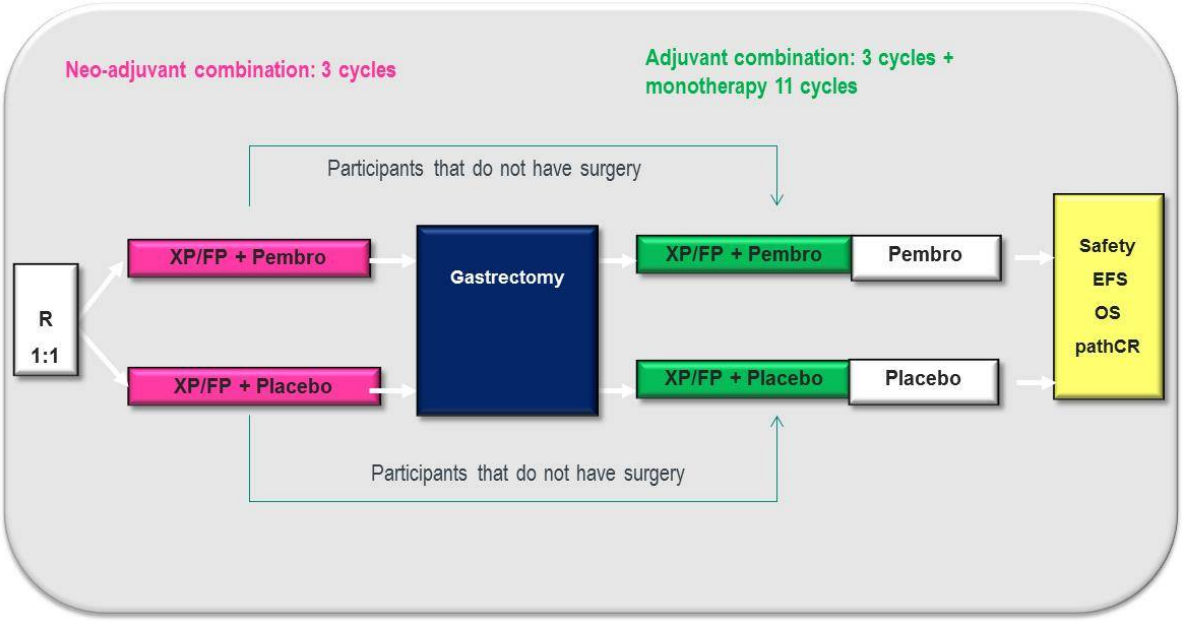

Figure 1 Main Study Diagram

5.1.2 FLOT Cohort

The FLOT Safety Cohort will be a double-blinded cohort, stratified by tumor staging, in which approximately 60 participants will be randomized to evaluate the combination of pembrolizumab with the chemotherapy backbone treatment known as FLOT (Table 2).

The safety cohort will open in a limited number of sites. Participants will be randomized in a 1:1 ratio to receive pembrolizumab + FLOT or placebo + FLOT. The safety cohort data will be evaluated after participants have completed surgical resection + 30 days post-surgical evaluation. Following review of the available safety data by the standing internal Data Monitoring Committee (siDMC), the FLOT regimen may be incorporated as one of the standard-of-care chemotherapy backbones in the main study.

As of Amendment 06, the FLOT Safety Cohort will be expanded to enroll 200 participants and will be designated the FLOT Cohort. Participants will be stratified using the same factors as the Main Study (XP/FP), see Section 7.3.1. Future interim analyses of the FLOT Cohort will be monitored by the external DMC.

The schedule of assessments is the same as described for the main study in Section 5.1.1.

Table 2 FLOT Cohort: Treatment Dose and Schedule

Neoadjuvant Combination Phase (3 cycles) and Adjuvant Combination Phase (3 cycles)
Group 1: FLOT + pembrolizumab 200 mg
Group 2: FLOT + placebo
Adjuvant Monotherapy Phase (11 cycles)
Group 1: pembrolizumab 200 mg
Group 2: placebo

Abbreviations: FLOT=docetaxel + oxaliplatin + 5-FU + leucovorin (calcium folinate).

1 treatment cycle=3 weeks duration (treatment cycles are based on pembrolizumab/placebo administration).

Pembrolizumab or placebo: administered on Day 1 of each treatment cycle every 3 weeks.

FLOT: Docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, 5-FU 2600 mg/m^2, and leucovorin (calcium folinate) 200 mg/m^2. The FLOT regimen will be administered every 2 weeks, for a total of 4 administrations in the neoadjuvant combination phase and 4 administrations in the adjuvant combination phase.

5.1.2.1 FLOT Cohort Diagram

The FLOT Cohort design is depicted in Figure 2.

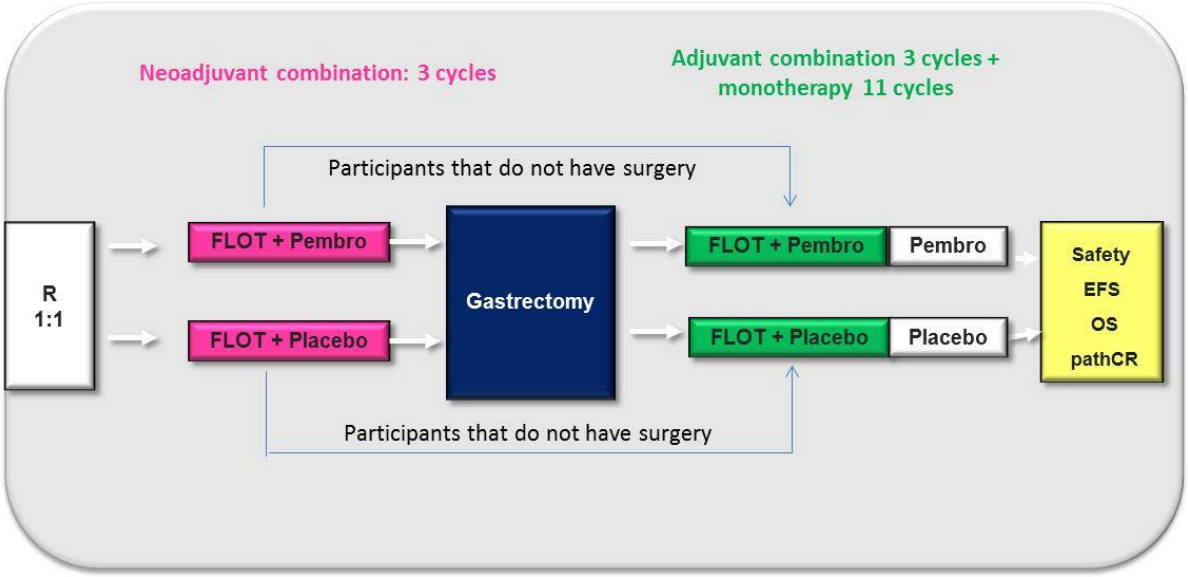

Figure 2 FLOT Cohort Diagram

5.2 Number of Participants

Approximately 1000 participants will be randomized in the entire study. Approximately 200 participants will be randomized in the FLOT cohort. Approximately 800 participants will be randomized in the Main Study (XP/FP). 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.

5.3 Beginning and End of Study Definition

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

5.3.1 Clinical Criteria for Early Study Termination

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, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

This study will use event-free survival (EFS), pathological complete response (pathCR), and overall survival (OS) as primary endpoints. Although OS is the standard endpoint for clinical studies, EFS and DFS are common surrogate endpoints for OS that are used to evaluate the efficacy of neoadjuvant and adjuvant cancer therapy and are sometimes used as primary endpoints [Martin, M., et al 2008] [Morschhauser, F., et al 2008] [Motzer, R. J., et al 2008] [Paridaens, R. J., et al 2008] [Sargent, D. J., et al 2005]. See Section 10.4, Analysis Endpoints for the primary and secondary endpoint definitions.

It is well established that pathCR following preoperative therapy is associated with improved survival in several malignancies, including breast adenocarcinoma after preoperative chemotherapy ± RT [Wolmark, N., et al 2001] [Symmans, W. F., et al 2007] [Adams, S., et al 2010] [Chavez-Macgregor, M., et al 2010], esophageal cancer after preoperative chemoradiotherapy [Berger, A. C., et al 2005] [Rohatgi, P. R., et al 2005] [Chao, Y. K., et al 2009] [Donahue, J. M., et al 2009] [Park, J. W., et al 2011], lung cancer after preoperative chemoradiotherapy [Mamon, H. J., et al 2005] [Chen, A. M., et al 2007]; and rectal cancer after preoperative chemoradiotherapy [Maas, M., et al 2010] [Pucciarelli, S., et al 2004].

Notably, the 15% to 27% rate of pathCR after chemoradiotherapy in rectal cancer [Maas, M., et al 2010] has led some groups to omit surgery and undertake intensive follow-up in select participants who achieve a clinical complete response with no detectable residual tumor after chemoradiotherapy [Habr-Gama, A., et al 2004].

The biology of tumors that completely regress with preoperative therapy is likely to be distinct from tumors that did not achieve a pathCR [Ajani, J. A. 2005] [Berger, A. C., et al 2005] and is reflected in EFS and OS. As demonstrated in other malignancies [Wolmark, N., et al 2001] [Adams, S., et al 2010] [Berger, A. C., et al 2005] [Rohatgi, P. R., et al 2005] [Chao, Y. K., et al 2009] [Donahue, J. M., et al 2009] [Park, J. W., et al 2011] [Maas, M., et al 2010] [Pucciarelli, S., et al 2004], patients with gastric/GEJ adenocarcinoma who achieve a pathCR following preoperative therapy have significant improvements in OS and recurrence-free survival [Fields, R.C., et al 2011], and DSS [Mansour, J. C., et al 2007].

5.4.1.2 Safety Endpoints

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

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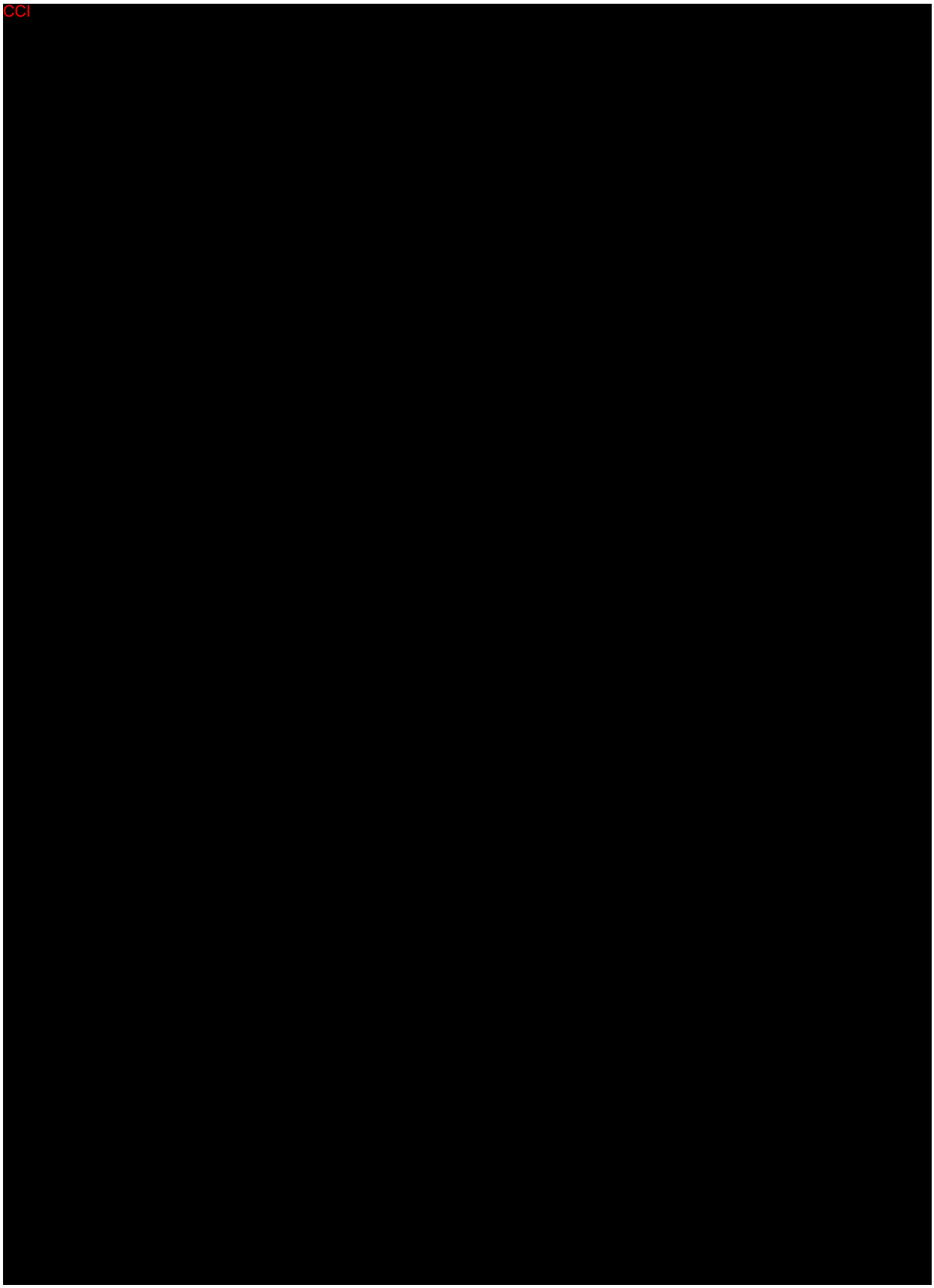

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5.4.2 Rationale for the Use of Chemotherapy/Placebo

5.4.2.1 Rationale for the Use of Cisplatin + Capecitabine or 5-FU in Gastric Cancer

Systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer with standard combination chemotherapy regimens containing cisplatin and capecitabine or 5-FU.

The V325 study [Van Cutsem, E., et al 2006] was a randomized Phase III study to compare docetaxel/cisplatin/5-FU with cisplatin + 5-FU (FP), and it showed statistically significant OS time (median 9.2 months and 8.6 months, respectively, p=0.02), PFS time (median 5.6 months and 3.7 months, respectively; p=0.001), response rate (37% and 25%, respectively; p=0.01) associated with docetaxel/cisplatin/5 FU. In terms of safety, the addition of docetaxel was associated with increased Grades 3 to 4 neutropenia (82% versus 57% with 5-FU/cisplatin alone), complicated neutropenia (29% versus 12%), Grades 3 to 4 diarrhea (19% versus 8%), and Grades 3 to 4 lethargy (19% versus 14%). The result of V325 supported the registration of docetaxel and docetaxel/cisplatin/5-FU as one of the standard regimens for the first-line treatment of gastric cancer. However, due in part to increased toxicity; incorporation of docetaxel into first-line gastric cancer regimens has been limited.

The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) study [Cunningham, D., et al 2006a] was a Phase III study to compare epirubicin + oxaliplatin + 5-FU [EOF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + cisplatin + 5-FU [ECF], and epirubicin + oxaliplatin + capecitabine [EOX] in advanced esophagogastric cancer. Overall survival was significantly longer among participants receiving EOX versus ECF (9.9 months, 9.3 months, 9.9 months, and 11.2 months for ECF, EOF, ECX, and EOX, respectively). No significant differences were observed in terms of response rate or PFS. As an outcome of the REAL-2 study, ECF became one of the popular regimens for first-line treatment of gastric cancer in the European Union. However, according to the European Society for Medical Oncology guideline (2013), the use of the triplet regimen should be limited because of increased toxicity. There are no Phase III studies directly comparing FP and ECF.

The ML17032 study [Ryu, M. H. and Kang, Y. K. 2009] compared XP with FP. The primary objective was to show noninferiority in terms of PFS time. Median PFS was 5.6 months among participants receiving XP and 5.0 months among participants receiving FP; median OS times were 10.5 months and 9.3 months, and ORR were 46% and 32%, in these groups, respectively. Based on this study, capecitabine has been approved in combination with a

platinum-based regimen for the first-line therapy of advanced gastric cancer in the United States and Japan.

The S-1 Plus cisplatin versus S-1 in RCT in the Treatment for Stomach cancer (SPIRITS) study [Koizumi, W., et al 2008] was a Phase III study to compare the oral fluoropyrimidine S-1 plus cisplatin versus S-1 in Japanese participants. Median OS was 13 months versus 11 months, respectively. Progression-free survival was 6 months versus 4 months, respectively; $p<0.001$). Based on these data, S-1 plus cisplatin became the most popular regimen for the first-line therapy of advanced gastric cancer in Japan.

The FLAGS study [Ajani, J. A., et al 2010] was a Phase III study to compare the oral fluoropyrimidine S-1 plus cisplatin versus 5-FU plus cisplatin in Western populations. The study failed to show superiority for S-1 plus cisplatin over FP; median OS was 8.6 months and 7.9 months for S-1/cisplatin and FP, respectively. More toxicity of S-1 and dose reduction due to AE was observed in Western populations.

In summary, platinum/fluoropyrimidine doublet regimens are the most broadly used for first-line chemotherapy regimen for advanced gastric cancer. The comparable efficacy of regimens substituting capecitabine for infused 5-FU has been directly studied in 2 Phase III studies: the REAL-2 study and the ML17032 study. The combination of infused or oral 5-FU is therefore recognized worldwide as one of the standard first-line chemotherapy regimens for participants with metastatic disease.

5.4.2.2 Rationale for Use of FLOT in Gastric Cancer

Docetaxel-based chemotherapy is effective in metastatic gastric and gastro-esophageal junction adenocarcinoma but had not previously been evaluated in the context of resectable patients [Van Cutsem, E., et al 2006].

FLOT4-AIO [Al-Batran, S. E., et al 2016] [Al-Batran, S. E., et al 2017] was a randomized, open-label, Phase II/III study in patients with resectable gastric or GEJ adenocarcinoma. Patients were assigned (1:1) to either 4 preoperative and 4 postoperative 2-week cycles of docetaxel 50 mg/m^2, intravenous oxaliplatin 85 mg/m^2, intravenous leucovorin 200 mg/m^2, and fluorouracil 2600 mg/m^2 as a 24-hour infusion, all on Day 1 (FLOT group), or 3 preoperative and 3 postoperative 3-week cycles of intravenous epirubicin 50 mg/m^2 on Day 1, intravenous cisplatin 60 mg/m^2 on Day 1, and either 5-FU 200 mg/m^2 as continuous intravenous infusion or capecitabine 1250 mg/m^2 orally (2 doses of 625 mg/m^2 per day) on Days 1 to 21 (ECF/ECX group).

Results are available online at www.clinicaltrials.gov (Identifier NCT01216644).

In the Phase II part of the study, FLOT was associated with significantly higher proportions of patients achieving pathological complete regression compared with ECF/ECX (16% [95% CI: 10–23] versus 6% [95% CI: 3–11]; p=0·02) [Al-Batran, S. E., et al 2016]. At least one SAE involving a perioperative medical or surgical complication was experienced by 25% of patients in the FLOT group versus 40% in the ECF/ECX group. The most common non-surgical Grade 3–4 AEs in the FLOT and ECF/ECX groups, respectively were neutropenia

(52% of patients versus 38%), leucopenia (28% versus 20%), infection (12% in both groups), fatigue (9% versus 14%), and vomiting (3% versus 10%).

In the Phase III part of the study, FLOT improved OS, with a median OS of 50 months versus 35 months for ECF/ECX; HR 0.77 [0.63-0.94]; p=0.012) [Al-Batran, S. E., et al 2017]. FLOT also improved PFS, with a median PFS of 30 months versus 18 months for ECF/ECX (HR: 0.75; 95% CI: 0.62-0.91; p=0.004). In the FLOT and ECF/ECX groups, respectively, perioperative complications were experienced by 51% of patients versus 50%, and the 30- and 90-day mortality rates were 2% and 5% versus 3% and 8%. There was more Grade 3/4 neutropenia with FLOT and more Grade 3/4 nausea and vomiting with ECF/ECX. In the FLOT and ECF/ECX groups, respectively, nonsurgical SAEs were experienced by 61% of patients versus 62%; dose modifications were performed for 40% versus 49% (pre-op dose modifications for 19% versus 31% and post-op dose modifications for 46% versus 56%); and discontinuations due to drug-related AEs for 10% versus 16% (provided by Al-Batran S, Institute of Clinical Cancer Research; data on file).

5.4.2.3 Safety Evaluation of Pembrolizumab + XP in KEYNOTE 059 Cohort 2

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, 67% were men, and the median age was 58 years old. As of the 09 OCT 2015 data cutoff date, median follow-up duration was 5.5 months (range 4.0 to 7.3). There were no treatment-related deaths and only 1 participant (6%) discontinued treatment because of an AE (stomatitis), which was considered by the investigator to be unrelated to pembrolizumab or chemotherapy. Seventeen participants (94%) experienced treatment-related AEs of any grade, most commonly stomatitis (n=7, 39%), decreased appetite (n=6, 33%), nausea (n=5, 28%), and neutropenia/decreased neutrophils (n=11, 61%) without neutropenic fever and unrelated to pembrolizumab. Twelve participants (67%) experienced Grades 3 to 4 treatment-related AEs; none were attributed to pembrolizumab. AEs attributed to pembrolizumab occurred in 7 participants (39%); the most common were diarrhea, dysgeusia, hyperthyroidism, and nausea (n=2 each); all were Grades 1 to 2. Eight participants (44%) experienced AEs of special interest, regardless of attribution by investigator, including hyperthyroidism, hypothyroidism, infusion-related reaction, pruritus, and vasculitis and all were Grades 1 to 2.

Based on these data, the combination of pembrolizumab, cisplatin, and fluoropyrimidine (capecitabine or 5-FU) has a manageable safety profile.

5.5 Justification for Dose

The dose recently approved in the United States for multiple indications is 200 mg Q3W. The pembrolizumab dose studied in KEYNOTE 012 that established efficacy in gastric cancer participants is 10 mg/kg Q2W, and recent studies in other tumor types have indicated that both 10 mg/kg Q2W and 200 mg Q3W are likely to be similar with regard to efficacy and tolerability.

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every Q2W representing an approximate 5 to 7.5 fold exposure range (refer to IB, Section 5.2.2);

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

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

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

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

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

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

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

6. Study Population

Male and female participants with previously untreated, locally advanced resectable gastric or GEJ adenocarcinoma of at least 18 years will be enrolled in this study.

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

6.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Have previously untreated localized gastric or GEJ adenocarcinoma as defined by T3 or greater primary lesion or the presence of any positive nodes - N+ (clinical nodes) without evidence of metastatic disease. Siewert type 2 or 3 tumors are eligible. Enrollment of participants with Siewert type 1 tumors will be limited to those for whom the planned treatment is perioperative chemotherapy and resection. Tumor staging prior to enrollment must consist of at least 1 imaging modality: computed tomography (CT) or magnetic resonance imaging (MRI).

Demographics

2. Be at least 18 years of age on the day of signing informed consent

3. Have an ECOG performance status of 0 to 1, to be performed within 3 days prior to the first dose of study treatment

4. Have a life expectancy of greater than 6 months

Male participants:

5. Male participants of childbearing potential must agree to use an adequate method of contraception as outlined in Appendix 3, for the course of the study through 180 days after the last dose of chemotherapy.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant

Female participants:

6. Female participants of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If

the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7. Female participants of childbearing potential must be willing to use an adequate method of contraception as outlined in Appendix 3, for the course of the study through 180 days after the last dose of chemotherapy or through 120 days after the last dose of pembrolizumab, whichever is greater.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Informed Consent

8. The participant 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.

Other Inclusions

9. Plan to proceed to surgery following pre-operative chemotherapy based on standard staging studies per local practice.

10. Be willing to provide tissue from a tumor lesion at baseline and at time of surgery

11. Have adequate organ function as defined in the following table (Table 3). Specimens must be collected within 10 days prior to the start of study treatment.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine and/or measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN and creatinine clearance ≥30 mL/min **OR** Creatinine clearance ≥60 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
INR **OR** PT aPTT/PTT	≤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); ANC=absolute neutrophil count; aPTT; activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; GFR=glomerular filtration rate; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal.

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

[b] CrCl should be calculated per institutional standard.

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

6.2 Exclusion Criteria

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

Medical Conditions

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

2. Has an active infection requiring systemic therapy.

3. Has a diagnosis of immunodeficiency.

4. 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.

5. Has a known severe hypersensitivity (≥ Grade 3) to pembrolizumab, its active substance and/or any of its excipients. (Refer to the respective IB for a list of excipients.)

6. Has a known severe hypersensitivity (≥ Grade 3) to any of the study chemotherapy agents and/or to any of their excipients.

7. 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.

8. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

9. 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.

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

11. Female participants: Is pregnant or breastfeeding or expecting to conceive children within the projected duration of the study, starting with the screening visit through180 days after the last dose of chemotherapy or through 120 days after the last dose of pembrolizumab, whichever is greater.

    Male participants: Is expecting to father children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of chemotherapy.

12. Has a history or current evidence of any condition (eg, known deficiency of the enzyme dihydropyrimidine dehydrogenase [DPD]), 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.

13. Has had an allogeneic tissue/solid organ transplant.

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

15. A woman of child-bearing potential (WOCBP) who has a positive urine pregnancy test within 72 hours prior to receiving first dose of study treatment (see Appendix 6). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (ie, CTLA-4, OX-40, CD137) or has previously participated in a MSD pembrolizumab (MK-3475) clinical study.

17. Has received prior systemic anti-cancer therapy including investigational agents for the current malignancy.

18. Is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study treatment.

19. Has received a live vaccine within 30 days prior to the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, *Bacillus Calmette–Guérin* (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

20. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

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

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

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

6.3.2 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.

6.4 Screen Failures

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

6.5 Participant Replacement Strategy

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

7. Treatments

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

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment. All supplies will be provided open label. Pembrolizumab (MK-3475) will be provided as non-kitted single vials or multiple vials in a kit box. Cisplatin, docetaxel, oxaliplatin, leucovorin (calcium folinate) and 5-FU will be provided as a kit with a single vial. Capecitabine will be provided as a kit with tablets in blister packs or bottles. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The treatments to be used in this study are outlined in Table 4. A cycle of treatment is 3 weeks (21 days) long and is set relative to pembrolizumab/placebo.

Regardless of clinical benefit, participants may only receive 17 administrations (approximately 1 year) of pembrolizumab.

Pembrolizumab and Placebo

Pembrolizumab or placebo will be administered on Day 1 of each 3-week cycle 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 of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. Pembrolizumab will be dosed and administered by blinded and qualified study site personnel.

The placebo will be a normal saline solution prepared by the unblinded pharmacist. The placebo will be dosed and administered by blinded and qualified study site personnel in the same manner as the investigational product (pembrolizumab).

XP/FP

Cisplatin 80 mg/m^2 will be administered as a 60- or 120-minute IV infusion or per site's standard practice on Day 1 of each treatment cycle, Q3W for 3 cycles in the neoadjuvant combination and 3 cycles in the adjuvant combination phases.

Capecitabine 1000 mg/m^2 will be administered orally 2 times a day (bid) from Day 1 to Day 14 of each treatment cycle, Q3W for 3 cycles in the neoadjuvant combination and 3 cycles in the adjuvant combination phases.

5-FU 800 mg/m^2/day will be administered as a continuous IV infusion from Day 1 to Day 5, for a total dose of 4000 mg/m^2 (120 hours, or per local standard) of each treatment cycle, Q3W for 3 cycles in the neoadjuvant combination and 3 cycles in the adjuvant combination phases.

FLOT

FLOT chemotherapy will be administered on Days 1 and 15 of Cycle 1; Day 8 of Cycle 2, and Day 1 of Cycle 3 in the neoadjuvant and adjuvant phases.

Docetaxel 50 mg/m^2 will be administered as a 60-minute IV infusion, or per site's standard practice.

Oxaliplatin 85 mg/m^2 will be administered as a 2-hour IV infusion, or per site's standard practice.

Leucovorin (calcium folinate) 200 mg/m^2 will be administered as a 2-hour IV infusion, or per site's standard practice.

5-FU 2600 mg/m^2 will be administered as a 24-hour infusion.

See Section 9.1.8.1 for timing of dose administration.

Table 4 Study Treatments

Study Treatment Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
Pembrolizumab/Placebo					
Pembrolizumab (MK-3475)	Solution for infusion	25 mg/mL	200 mg on Day 1 of each cycle (Q3W)	IV infusion	Provided centrally by the Sponsor
Placebo (normal saline)	Solution for infusion	N/A	On Day 1 of each cycle (Q3W)	IV infusion	Provided locally by the study site, subsidiary, or designee
XP/FP					
Cisplatin	Solution for infusion	1 mg/mL	80 mg/m^2 on Day 1 of each cycle (Q3W)	IV infusion	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Capecitabine	Tablet	150 mg & 500 mg	1000 mg/m^2 bid on Days 1-14 of each cycle (Q3W)	Oral	
5-FU	Solution for infusion	25 mg/mL & 50 mg/mL	800 mg/m^2/day continuous on Days 1-5 of each cycle (Q3W) (120 hours, or per local standard)	IV infusion	
FLOT					
Docetaxel	Solution for infusion	20 mg/mL	50 mg/m^2 on Days 1 and 15 of Cycle 1, Day 8 of Cycle 2, and Day 1 of Cycle 3 (Q2W)	IV infusion	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Oxaliplatin	Solution for infusion	5 mg/mL	85 mg/m^2 on Days 1 and 15 of Cycle 1, Day 8 of Cycle 2, and Day 1 of Cycle 3 (Q2W)	IV infusion	
5-FU	Solution for infusion	50 mg/mL	2600 mg/m^2 on Days 1and 15 of Cycle 1, Day 8 of Cycle 2, and Day 1 of Cycle 3 (Q2W)	IV infusion	
Leucovorin (calcium folinate)	Solution for infusion	10 mg/mL	200 mg/m^2 on Days 1 and 15 of Cycle 1, Day 8 of Cycle 2, and Day 1 of Cycle 3 (Q2W)	IV infusion	

5-FU=5-fluorouracil; bid=2 times a day; IV=intravenous; N/A=not applicable; Q2W=every 2 weeks; Q3W=every 3 weeks.

The body surface area (BSA) in m^2 should be calculated per local guidance.

Chemotherapy backbones include XP (cisplatin + capecitabine), FP (cisplatin + 5 FU), or FLOT (docetaxel + oxaliplatin + 5-FU + leucovorin [calcium folinate]).

The investigator will decide the chemotherapy backbone (XP or FP or FLOT) prior to randomization. Participants will continue on the chemotherapy chosen prior to randomization throughout the study and will not be allowed to switch between chemotherapy treatments (exception may be granted after Sponsor consultation, e.g., participants who have difficulty swallowing oral study treatment).

All supplies indicated in Table 4 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

7.2 Dose Modification (Escalation/Titration/Other)

If appropriate, the investigator may attribute each toxicity event to any of the components in the neoadjuvant and/or adjuvant combination treatment groups.

Pembrolizumab and placebo dose reductions are not permitted. Pembrolizumab and placebo treatment may only be interrupted or discontinued due to toxicity. For participants requiring a dose modification of standard of care chemotherapy, the next cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to ≤ Grade 1 or to the baseline status of the participant.

If a dose reduction for toxicity occurs with any chemotherapy agent, the dose may not be re-escalated. Participants may have a maximum of 2 dose reductions (if applicable) for chemotherapy agents throughout the course of combination neoadjuvant and/or adjuvant treatment phases for toxicities. Participants who require a third dose reduction will have that chemotherapy agent discontinued. If a participant experiences several toxicities and there are conflicting recommendations, please follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

During the neoadjuvant and/or adjuvant phases, the reduction of the dose of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If 1 chemotherapy agent must be held, it is recommended to hold all study treatments and delay the entire cycle until the toxicity resolves according to the guidelines in Sections 7.2.2, 7.2.3, 7.2.4. If a cycle is delayed, all subsequent cycles must be adjusted/delayed accordingly, to account for the initial delay.

If, in the opinion of the investigator, the toxicity is related to the combination of chemotherapy agents, all drugs should be reduced according to the recommended dose modifications. If the toxicity is related to the combination of all agents, chemotherapy should be reduced, interrupted, or discontinued; pembrolizumab or placebo should be interrupted or discontinued according to the recommended dose modifications.

If participants have severe AEs requiring discontinuation of any agents in the standard of care chemotherapy treatment(s), the Sponsor must be consulted prior to the discontinuation.

Neoadjuvant and adjuvant treatment may be altered according to the dose modification guidelines (Table 5 to Table 11). If toxicity is not otherwise specified, investigators should refer to the label or local guidelines for standard of care chemotherapy dose adjustments. If,

in the opinion of the investigator, a dose modification for a non-specified toxicity would benefit the participant, this may be done.

The CTCAE v4.0 must be used to grade the severity of AEs. All dose modifications will be based on the AE requiring the greatest dose modification. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

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 (pembrolizumab) and Section 7.7.3.

Table 5 Dose Modifications for Chemotherapies + Pembrolizumab or Placebo

	Dose level 0	**Dose level -1**	**Dose level -2**	**Dose level -3**
pembrolizumab or placebo	200 mg fixed dose	Dose reductions are not permitted.	Dose reductions are not permitted.	Dose reductions are not permitted.
XP/FP				
cisplatin	80 mg/m^2	60 mg/m^2	40 mg/m^2	Discontinue
capecitabine	1000 mg/ m^2 bid	750 mg/m^2 bid	500 mg/m^2 bid	Discontinue
5-FU	800 mg/m^2/day	600 mg/m^2/day	400 mg/m^2/day	Discontinue
FLOT*				
oxaliplatin	85 mg/m^2	Reduce to 75%	Reduce to 50%	Discontinue
docetaxel	50 mg/ m^2	Reduce to 75%	Reduce to 50%	Discontinue
5-FU	2600 mg/m^2	Reduce to 75%	Reduce to 50%	Discontinue

The body surface area (BSA) in m^2 should be calculated per local guidance.

*Dose reduction is not needed for leucovorin (calcium folinate).

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

Refer to Appendix 9, Section 12.9.1 for country-specific requirements.

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

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

included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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 reactions 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 pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

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

CTCAE=Common Toxicity Criteria for Adverse Events; IV=intravenous; NCI= National Cancer Institute; NSAID=non-steroidal anti-inflammatory drug; po=per OS (orally)

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v4.0 at http://ctep.cancer.gov.

Other allowed dose interruption for pembrolizumab

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

7.2.2 Dose Modifications for Cisplatin and Capecitabine or 5-FU

Please refer to criteria for cisplatin and capecitabine or 5-FU dose modification included in Table 8 and Table 9.

Table 8 Dose Modification Guidelines for Cisplatin Drug-related Adverse Events

Category	Toxicity	Hold Cisplatin Treatment for Grades	Timing for Restarting Cisplatin Treatment	Dose for Restarting Cisplatin Treatment	Discontinue Cisplatin
Hematologic	Neutropenia[1]	3[1]	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[1]	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[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
		4[1]	N/A	Discontinue	Permanently discontinue cisplatin
	Thrombo-cytopenia	3-4[1]	Platelet count resolves to >75,000/mm^3 or baseline	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[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
	Ototoxicity or Sensory neuropathy	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded
	Laboratory Adverse Events	4[1]	Toxicity resolves to Grade 0-1	Reduce by1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 DL reductions exceeded

DL=dose level; G-CSF=granulocyte colony-stimulating factor.

[1] Permanent discontinuation should be considered for any severe or life-threatening event.

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

Table 9 Dose Modification Guidelines for Capecitabine or 5-FU Drug-related Adverse Events

Category	Toxicity	Hold Capecitabine or 5-FU Treatment for Grade	Timing for Restarting Capecitabine or 5-FU Treatment	Dose for Restarting Capecitabine or 5-FU Treatment	Discontinue Capecitabine or 5-FU
Hematologic	Neutropenia	3[1]	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[1]	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[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
		4[1]	N/A	Discontinue	Permanently discontinue
	Thrombocytopenia	3-4[1]	Platelet count resolves to >75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
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[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded
	Laboratory adverse events	4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if >2 DL reductions exceeded

DL=dose level; 5-FU=5-fluorouracil; G-CSF=granulocyte colony-stimulating factor; N/A=not applicable.

[1] Permanent discontinuation should be considered for any severe or life-threatening event.

[2] Participants with intolerable or persistent Grade 2 drug-related adverse event 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 Grades 0-1 within 12 weeks of the last dose.

7.2.3 Dose Modification Guidelines for Docetaxel

Please refer to criteria for docetaxel dose modification included in Table 10.

Table 10 Dose Modification Guidelines for Docetaxel Drug-related Adverse Events

Category	Toxicity	Hold Docetaxel Treatment for Grade	Timing for Restarting Docetaxel Treatment	Dose for Restarting Docetaxel Treatment	Discontinue Docetaxel
Hematologic	Neutropenia	1-4 lasting ≤7 days	ANC resolves to ≥1500/mm^3	N/A	N/A
		4 lasting >7 days, 1st occurrence	ANC resolves to ≥1500/mm^3	Reduce by 1 DL	N/A
		4 lasting >7 days, 2nd occurrence	ANC resolves to ≥1500/mm^3	Reduce by 2 DL	N/A
		4 lasting >7 days, 3rd occurrence	N/A	N/A	Yes
	Febrile neutropenia (defined as T ≥100.5°F and ANC ≤ 1,000/mm^3)	1st occurrence	ANC resolves to ≥1500/mm^3	Reduce by 1 DL *Consider G-CSF for subsequent cycles	N/A
		2nd occurrence	ANC resolves to ≥1500/mm^3	Reduce by 2 DL *G-CSF highly recommended	N/A
		3rd occurrence	N/A	N/A	Yes
	Thrombocytopenia	1-3	Platelet count resolves to >100,000/mm^3	N/A	N/A
		4, 1st occurrence	Platelet count resolves to >100,000/mm^3	Reduce by 1 DL	N/A
		4, 2nd occurrence	Platelet count resolves to >100,000/mm^3	Reduce by 2 DL	N/A
		4, 3rd occurrence	N/A	N/A	Yes
	Anemia	1-3	Until anemia resolves to Grade 1 or baseline	N/A	N/A
		4, 1st occurrence	Until anemia resolves to Grade 1 or baseline	Reduce by 1 DL	N/A
		4, 2nd occurrence	Until anemia resolves to Grade 1 or baseline	Reduce by 2 DL	N/A
		4, 3rd occurrence	N/A	N/A	Yes

Category	Toxicity	Hold Docetaxel Treatment for Grade	Timing for Restarting Docetaxel Treatment	Dose for Restarting Docetaxel Treatment	Discontinue Docetaxel
Non-hematological toxicity and other hematological toxicity not described above**	All	1-2	No	None	N/A
		3-4, 1st occurrence	Yes, until toxicity resolves to Grade 0-1	Reduce by 1 DL	N/A
		3-4, 2nd occurrence	Yes, until toxicity resolves to Grade 0-1	Reduce by 2 DL	N/A
		3-4, 3rd occurrence	N/A	N/A	Yes
	Peripheral neuropathy	1-2	No	Reduce by 1 DL	N/A
		3-4	N/A	N/A	Discontinue upon onset

DL=dose level; G-CSF=granulocyte colony-stimulating factor; N/A=not applicable.

*In order to avoid treatment delays, **secondary prophylaxis with G-CSF** will be required for all subsequent cycles if one of the following criteria is applicable:

- occurrence of febrile neutropenia or infection in neutropenia at any time or;
- occurrence of a NCI-CTC grade 4 neutropenia or;
- delay of one therapy cycle because of leukopenia or neutropenia by more than 3 days.

**Participants who experience suspected severe hypersensitivity reaction to docetaxel (eg, generalized rash/erythema, hypotension and/or bronchospasm, angioedema or anaphylaxis) should be discontinued from docetaxel

7.2.4 Dose Modification Guidelines for Oxaliplatin

Please refer to criteria for docetaxel dose modification included in Table 11.

Table 11 Dose Modification Guidelines for Oxaliplatin Drug-related Adverse Events

Category	Toxicity	Grade	Hold until	Dose for Restarting Oxaliplatin Treatment
Hematologic	Neutropenia	3	Neutrophil count resolves to ≥1,500/mm^3	No reduction *consider G-CSF
		4	Neutrophil count resolves to ≥1,500/mm^3	Reduce by 1 DL *recommend G-CSF
	Febrile neutropenia	3, 1st occurrence	Neutrophil count resolves to ≥1,500/mm^3	Consider G-CSF
		3, 2nd occurrence	Neutrophil count resolves to ≥1,500/mm^3	Dose reduce by 1 DL *recommend G-CSF
		Further occurrences	Neutrophil count resolves to ≥1,500/mm^3	Dose reduce by 2 DL *recommend G-CSF
	Thrombocytopenia with bleeding	3-4	Platelet count resolves to >100,000/mm^3	Reduce by 1 DL
Non-hematologic	Neurotoxicity	Cold-induced dysesthesia	N/A	N/A
		Paresthesia ≤7 days	N/A	N/A
		Paresthesia <7-14 days	N/A	N/A
		Paresthesia-persistent	N/A	Reduce 1DL
		Paresthesia with pain 7-14 days	N/A	Reduce 1DL
		Persistent Paresthesia with pain	N/A	Reduce 2DL or discontinue
		Paresthesia with functional impairment	N/A	Reduce 2DL if lasting 7-14 days or discontinue if persistent
	All other non-hematologic toxicities**	3-4,1st occurrence	N/A	Reduce by 1 DL
		3-4, 2nd occurrence	N/A	Reduce by 2 DL

DL=dose level; G-CSF=granulocyte colony-stimulating factor; N/A=not applicable.

*In order to avoid treatment delays, **secondary prophylaxis with G-CSF** will be required for all subsequent cycles if one of the following criteria is applicable:

- occurrence of febrile neutropenia or infection in neutropenia at any time or;
- occurrence of a NCI-CTC grade 4 neutropenia or;
- delay of one therapy cycle because of leukopenia or neutropenia by more than 3 days

**Permanent discontinuation should be considered for any severe or life-threatening event. Participants with intolerable or persistent Grade 2 drug-related AEs 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 Grades 0-1 within 12 weeks of the last dose.

7.2.5 Dose Modification for Adjuvant Therapy

Dose modifications are permitted in the study as per Table 5. If participants were treated at reduced doses in the pre-operative phase of the study, the same standard of care chemotherapy doses will be re-initiated or continued in the post-operative treatment phase. Re-escalation of doses is not permitted. Once post-operative treatment is initiated, further modification of the study medications will be based on AEs as per Table 5, and specific reasons for dose modification must be documented.

If AEs warrant discontinuation of a study medication, the Sponsor must be consulted and a decision can be made on a case by case basis.

7.3 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab + chemotherapy or placebo + chemotherapy, respectively.

The chemotherapy regimen chosen by the investigator will be entered into IVRS/IWRS prior to treatment randomization assignment by the system.

7.3.1 Stratification

Treatment randomization will be stratified according to the following factors in the Main Study (XP/FP) and FLOT Cohort:

1. Geographic regions: Asia versus Non-Asia
2. Tumor staging: II versus III versus IVa
3. Backbone chemotherapy XP/FP versus FLOT

7.4 Blinding

A double-blinding technique will be used. Pembrolizumab (MK-3475) 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 treatment administration or clinical evaluation of the participants are unaware of the group assignments.

Chemotherapy administration will be open label.

See Section 9.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Standard of care chemotherapies will be prepared and administered as per the approved product labels. The body surface area (BSA) in m^2 should be calculated per local guidance.

7.5.2 Handling, Storage and Accountability

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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

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

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

7.6 Treatment Compliance

As participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering study medications are provided in the Pharmacy Manual.

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 Sec. 7.2.1 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruption of pembrolizumab.

7.7 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 therapy or vaccination may be required. The investigator is to discuss prohibited medications 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 treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

7.7.1 Acceptable Concomitant Medications/Therapy

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

During the adjuvant period, participants that do not have surgery or those with R1/R2 resection, may continue protocol planned adjuvant treatment (including pembrolizumab/placebo) and will be permitted to have radiation therapy (RT). Radiation therapy is in addition to and at the discretion of the site PI, but not part of protocol-specified therapy. If radiation therapy is used, all sites should follow the guidelines below in addition to applicable local guidelines and published standards in this disease [Smalley, S. R., et al 2012] [Stumpf, P. K., et al 2017]:

a. Do not administer radiation therapy concurrent with protocol-specified adjuvant combination chemotherapy (consisting of cisplatin, a fluoropyrimidine and pembrolizumab/placebo) at protocol-specified dosages.

b. If indicated, radiation therapy should be started and completed either:

   -Prior to initiation of protocol-specified adjuvant combination chemotherapy – or –

   -Following completion of protocol-specified adjuvant combination chemotherapy (estimated to be 3 cycles) and prior to initiation of adjuvant monotherapy consisting of pembrolizumab/placebo.

All concomitant medications received within 30 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 9.3.7.

7.7.2 Prohibited Concomitant Medication/Therapy

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phases of this study. Restrict the use of prohibited medications at least 14 days prior to the start of therapy:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy during the neo-adjuvant treatment phase
- Live or live-attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Administration of killed vaccines is allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event that is suspected to have an immunologic etiology. The use of systemic glucocorticoids for the management of chemotherapy-related toxicities and for the management of surgical events in the post-operative period may be allowed after consultation with the Sponsor. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

For participants taking capecitabine or 5-FU:

- Brivudine, sorivudine analogues, and other inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD).

For participants taking cisplatin:

- Phenytoin should not be started with cisplatin therapy.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment. Participants may receive other medications that the investigator deems to be medically necessary.

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.
- Caution is advised with the use of CYP2C9 substrates in participants taking capecitabine. The guidelines within the local label should be followed.
- Administration of leucovorin (calcium folinate) concomitantly with folic acid antagonists such as co-trimoxazole or pyrimethamine may reduce their effectiveness or even eliminate it.
- Leucovorin (calcium folinate) may reduce the effects of anticonvulsants, such as phenobarbital, primidone or phenytoin.

The Exclusion Criteria describes other medications which are prohibited during the treatment phase of this study.

7.7.3 Rescue Medications and Supportive Care

7.7.3.1 Supportive Care Guidelines for Immune-related Adverse Events

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2.

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.

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

Refer to Table 6 for supportive care guidelines for the following:

- Pneumonitis
- Diarrhea/Colitis
- Type 1 diabetes mellitus or hyperglycemia
- Hypophysitis
- Hyperthyroidism or Hypothyroidism

- Elevated liver functions
- Nephritis and renal dysfunction
- Myocarditis
- Other immune-related AEs

Refer to Table 7 for supportive care guidelines for the following:

- Management of Infusion Reactions

7.7.3.2 Supportive Care Guidelines for Cisplatin

Attempts should be made to control nausea and vomiting using non-steroidal therapies whenever possible. It is recommended that the participant be provided adequate anti-emetic regimens that will enable the administration of the prescribed doses of chemotherapy, with every effort to adhere to the protocol specified chemotherapy. To achieve this goal, the use of systemic glucocorticoids may be allowed after consultation with the Sponsor.

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

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

In addition, anti-emetic therapies listed in Table 12 may be used. Please refer to the product label or local standards of care for additional cisplatin supportive measures.

7.7.3.3 Supportive Care Guidelines for Capecitabine

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

7.7.3.4 Supportive Care Guidelines for 5-FU

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

7.7.3.5 Supportive Care Guidelines for the FLOT Regimen

Suggested anti-emetic therapy is provided in Table 12 (provided by Al-Batran S, Institute of Clinical Cancer Research; data on file). Attempts should be made to control emesis/nausea using non-steroidal therapies; however, the use of systemic glucocorticoids may be allowed after consultation with the Sponsor.

Please refer to the appropriate product label or local standards of care for additional docetaxel, oxaliplatin, and leucovorin (calcium folinate) supportive measures.

Table 12 Antiemetic Therapy

Day	Drug Class	Example
D1 (approx. 1 hour before chemotherapy) (acute emesis)	Neurokinin-1-receptor-antagonist and 5-HT3-receptor-antagonists	1 capsule Akynzeo (300 mg netupitant + 0.5 mg palonosetron), with or without food
D2 to D3 (delayed emesis)	5-HT3-receptor-antagonists	Alternatives: granisetron 2 mg PO/ 1 mg IV ondansetron 16-24 mg PO/ 8 mg IV tropisetron 5 mg PO/ IV dolasetron 200 mg PO/ 100 mg IV palonosetron 0.5 mg PO/ 0.25 mg IV
Approx.=approximately: D=day of therapy; IV=intravenous; PO=per os (orally)		

7.8 Treatment After the End of the Study

Upon study completion, participants are to be discontinued and may be enrolled in an extension study.

7.9 Clinical Supplies Disclosure

This study is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified study site personnel will be used to blind supplies. Study treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 9.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IRT) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.10 - Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the study, should such action be warranted.

7.10 Standard Policies

Study site personnel will have access to a central electronic treatment allocation/randomization system (IRT system) to allocate participants, to assign treatment to participants and to manage the distribution of clinical supplies.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment regimen will still continue to participate in the study as specified in Section 2 and Section 9.10.3.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- Radiographic disease progression outlined in Section 9.2.1.2 (after Sponsor communication, the investigator may elect to continue treatment)
- Unacceptable adverse experiences as described in Section 9.3 and Appendix 4
- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- A confirmed positive serum pregnancy test

- Investigator's decision to withdraw the participant

For participants who are discontinued from study treatment but continue to be monitored in the study, see Section 2 and Section 9.10.3 for those procedures to be completed at each specified visit.

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

8.2 Withdrawal from the Study

If a participant repeatedly fails to return for scheduled visits and/or if the study site is unable to contact the participant after multiple attempts (ie, is lost to follow-up), the procedures to be performed are outlined in Section 8.3.

If a participant decides not continue receiving study intervention, the participant is to be encouraged to continue visits in the study for follow-up, imaging, and vital status assessment.

Participants who withdraw consent during the study

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

Section 9.1.9 delineates the specific procedures performed at the time of withdrawal and withdrawal from future biomedical research.

Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3.

8.3 Lost to Follow Up

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

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

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The Investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

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

9.1 Administrative and General Procedures

9.1.1 Informed Consent

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

9.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial

protocol title, dated signature, and agreement of the participant (or their legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial informed consent form, any subsequent revised informed consent form, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or their 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 or the participant's legally acceptable representative's dated signature. Specifics about the study and the study population are to be included in the study informed consent form.

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

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the 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 before performing any procedure related to future biomedical research.

9.1.2 Inclusion/Exclusion Criteria

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

9.1.3 Participant Identification Card

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

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

9.1.4 Medical History

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

Please note that if the participant has lost at least 15 lbs (6.8 kg) over the 3 months prior to screening, "weight loss" should be entered as an active condition on the Medical History. As well, any autoimmune disorders, regardless of onset date, should be recorded.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before starting study treatment. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

9.1.5.2 Concomitant Medications

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

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

9.1.6 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.10.1.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a

treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

9.1.8 Treatment Administration

Study treatment will be administered by the investigator or designee according to the specifications within the Pharmacy manual.

Study Treatment should begin within 3 days of treatment allocation/randomization.

9.1.8.1 Timing of Dose Administration

Study treatment will begin on Day 1 of each 3-week dosing cycle after all procedures/assessments have been completed as detailed on the SoA (Section 2). Study treatments may be administered up to 3 days before or after the scheduled day of administration.

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

For the combination portions of the study, treatment will be administered in the order presented below:

- XP/FP + pembrolizumab or placebo: Pembrolizumab or placebo infusion is administered first, followed by the cisplatin infusion, and then oral capecitabine or 5-FU infusion.

- FLOT + pembrolizumab or placebo: Pembrolizumab or placebo infusion is administered first followed by FLOT. Of the FLOT chemotherapies, docetaxel should be administered first. Oxaliplatin should be administered before 5-FU. Oxaliplatin and leucovorin (calcium folinate) may be administered concurrently using a Y-line placed directly at the site of infusion; however, the drugs should not be mixed in the same infusion bag.

Treatment may continue with pembrolizumab + chemotherapy or placebo + chemotherapy until the participant receives the full protocol allowed cycles (3 neoadjuvant + 14 adjuvant) or documented disease progression/recurrence, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, or administrative reasons requiring cessation of treatment.

Note: Dosing interruptions are permitted in the case of medical or surgical events or logistical reasons (ie, elective surgery, unrelated medical events, participant vacation, and holidays) not related to study therapy. Participants should be placed back on study therapy as soon as clinically appropriate per the investigator, and not exceeding 3 weeks from the interrupted dosing. If a participant's dosing has been interrupted for more than 3 weeks, a Sponsor consultation must occur and be documented before participant can be placed back

on study therapy. Day 1 of subsequent cycles should be adjusted accordingly to adhere to every 3-week dosing schedule. The reason for interruption must be documented in the participant's study record.

Capecitabine

The evening dose of capecitabine should be taken approximately 12 hours after the morning dose and should be taken with food or within 30 minutes after food or a meal, with approximately 200 ml of water. Please refer to the product label for additional guidance on administration procedures for capecitabine. Note that if a participant is dosed later in the day, it is acceptable for only 1 dose to be taken on Day 1 of the cycle. Dosing 2 times a day may resume on Days 2 to 14 and the final dose will be taken in the morning of Day 15.

See also Section 7.1 for additional information on treatments administered.

9.1.9 Discontinuation and Withdrawal

Participants who withdraw consent from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal.

The End of Treatment and Follow-up visit procedures are listed in the SoA (Section 2) and Section 9.10 (Visit Requirements). After the end of treatment, each participant will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anti-cancer therapy, whichever occurs first, as described in Section 9.3.1). Participants who discontinue for reasons other than disease progression/recurrence will have post-treatment follow-up imaging for disease status until disease progression/recurrence, initiating a non-study cancer treatment, withdrawing consent, pregnancy, or end of study, whichever occurs first. After documented disease progression/recurrence each participant will be followed by telephone for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

9.1.9.1 Withdrawal From Future Biomedical Research

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

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between

the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

9.1.10 Procedures for Negative Studies Without Safety Concerns

If the study or a study intervention group discontinues due to futility or the study does not demonstrate statistically significant efficacy results per protocol-specified analyses without any urgent safety issues, one or more of the following actions may occur:

- unblinding of the participants' treatment assignment (see Section 9.1.11 blinding/unblinding).
- stopping treatment with placebo.
- discontinuing participants assigned to a specific control group (see Sections 8.1 and 9.1.9) or study intervention group unless participants are deriving clinical benefit (see Section 9.1.11).
- participants may be discontinued from parent study and may be enrolled into an extension study using pembrolizumab/study intervention if participants are deriving clinical benefit.

The investigator or medically qualified designee must inform each participant of these results and discuss treatment options.

9.1.11 Participant Blinding/Unblinding

Participants on treatment after IA3 was conducted have been unblinded to study intervention to facilitate in a decision by the investigator and participant whether to continue study intervention. The investigator may consider continuing study intervention for the participant, in consultation with the Sponsor, if the participant is benefitting from the study intervention and it is in their best interest to continue (see Section 9.1.10).

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

For emergency situations where the investigator or delegate 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 delegate 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 or delegate must enter the toxicity grade of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart.

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician should continue to be monitored in the study.

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

Study treatment identification information is to be unmasked ONLY if necessary for the welfare of the participant. Every effort should be made not to unblind the participant unless necessary.

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.

If there is an adverse event necessitating discontinuation of treatment and unblinding for appropriate clinical management of complications: the Sponsor's Clinical Director must be consulted to review the unblinding request documented on the Sponsor consultation form (SCF), in order to provide guidance on clinical management and diagnostic procedures. The emergency unblinding call center will not perform these intentional unblinds. The investigator must use the IRT system. Once an intentional unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

In the event of disease progression/recurrence with discontinuation from protocol treatment and unblinding required for participant(s) considered for enrollment on an alternate immuno-oncologic protocol that requires knowledge of prior treatment with pembrolizumab: prior to unblinding, the Sponsor's Clinical Director must be consulted to review the unblinding request documented on the Sponsor Consultation Form (SCF). The emergency unblinding call center will not perform these intentional unblinds. The investigator must use the IRT system. Once an intentional unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

9.1.12 Calibration of Equipment

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

9.2 Efficacy Assessments

9.2.1 Tumor Scans 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. Magnetic resonance imaging should be used only when CT is contraindicated or for scan of the brain. The same scan technique regarding modality and the use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden.

All scans used to assess tumor burden from the sites will be sent to the iCRO.

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

9.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of randomization. These scans will be considered the baseline assessment for the study. Chest, abdomen, and pelvis are to be scanned.

Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality, include all required anatomy, and performed within 28 days prior to randomization.

9.2.1.2 Tumor Scans During the Study

The first on-study scan will be performed after completion of 3 cycles of pre-operative therapy, at approximately 9 weeks (± 7 days) after the first dose of study treatment, before surgery (or earlier if clinically indicated). If there is a delay in the pre-operative treatment, the scan should be delayed until completion of pre-operative treatment. Participants who undergo surgery will have a post-surgery baseline scan. For participants who continue into the adjuvant treatment phase, the post-surgery baseline scan must be completed within 2 weeks prior to the first dose of the adjuvant treatment. Participants who undergo surgery are followed by scans every 12 weeks (± 7 days) from the post-surgery baseline scan. During the post-operative adjuvant phase, scans will be performed with assessments based on disease recurrence. Two years (24 months) after the date of the post-surgery baseline scan, the scan schedule will be reduced to every 24 weeks (± 7 days).

Participants who do not undergo surgery will be followed by scans every 12 weeks (± 7 days) from the post-neoadjuvant scan. The schedule will be reduced to every 24 weeks (± 7 days), 2 years after the post-neoadjuvant scan.

Scan timing after the first on-study assessment should follow calendar days and should not be adjusted for delays in cycle starts. Scans should continue to be performed until disease progression/recurrence, the start of new anti-cancer treatment, withdrawal of consent, or death, whichever occurs first.

Partial response, complete response, or disease recurrence will be evaluated per RECIST 1.1 [Eisenhauer, E. A., et al 2009].

Participants may continue treatment and follow the regular scan schedule intervals until documented disease progression/recurrence, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. If indicated, repeat scans to confirm progression may be performed at least 4 weeks after site assessed first radiologic evidence of PD in clinically stable participants (per irRECIST). Participants who have confirmed disease progression, as assessed by the site, may discontinue study treatment as clinically appropriate. Exceptions are detailed in Section 9.2.1.5.

9.2.1.3 End of Treatment and Follow-up Tumor Scans

For participants who discontinue study treatment early (before completing 14 cycles of treatment), tumor scans should be performed at the time of treatment discontinuation (±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then scan at treatment discontinuation is not mandatory.

- For participants who discontinue study treatment due to documented disease progression/recurrence, this is the final required tumor scan.

- For participants who discontinue study treatment without documented disease progression/recurrence, every effort should be made to continue monitoring disease status by tumor scan until disease progression/recurrence, initiating a non-study cancer treatment, withdrawing consent, pregnancy, or end of study, whichever occurs first.

  -If a previous scan was obtained within 4 weeks of treatment discontinuation, a new scan is not needed. The participant can continue on the same scan schedule used while on treatment. (See section 9.2.1.2)

  -If the participant has a new scan at the time of treatment discontinuation, this will serve as the end of treatment scan. The scan schedule will reset and continue every 12 weeks (± 7 days) after the end of treatment scan until 2 years after the post-surgery scan or the post-neoadjuvant scan (depending on whether the participant had surgery), after that the schedule will be reduced to every 24 weeks (± 7 days).

9.2.1.4 RECIST 1.1 Assessment of Disease

CT scan or MRI will be performed for assessment of disease progression/recurrence. RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of

disease progression/recurrence, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study therapy).

If indicated, biopsy confirmation of recurrent lesions will be performed.

All scans used to assess tumor burden should be submitted to the iCRO for disease evaluation centrally.

9.2.1.5 irRECIST Assessment of Disease

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by the site investigator/local radiology reviewers to assess tumor response and progression and make treatment decisions. These data will be collected in the clinical database. In this study, irRECIST will only be applied for disease evaluation during the neoadjuvant phase and continued throughout treatment for those participants who did not proceed to surgery.

If applicable to the assessment of the participant, study treatment should not be discontinued until progression is confirmed by the local site investigator/radiology assessment and after discussion with the Sponsor. 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. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing nontarget lesion(s)
- Development of new lesion(s)

For participants who have shown initial evidence of radiological PD by RECIST 1.1, it is at the discretion of the PI whether to continue a participant on study medication until repeat scans are obtained (using irRECIST for participant management (see Table 13). This clinical judgment decision by the site investigator should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may receive study medication and the tumor assessment should be repeated ≥4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Any participant deemed clinically unstable should be discontinued from study treatment at first radiologic evidence of PD and is not required to have repeat scans for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and nontarget lesions, as well as any incremental new lesion(s).

Disease progression will be considered to be "not confirmed" at repeat scan if ALL of the following occur (as assessed by irRECIST):

- Non-target disease resulting in initial PD is stable or qualitatively improved
- New lesion resulting in initial PD is stable or qualitatively improved
- No incremental new lesion(s) since last evaluation
- No incremental new non-target lesion progression since last evaluation

If repeat scan does not confirm PD per irRECIST as assessed by the local site investigator and the participant continues to be clinically stable, treatment may continue and follow the regular scan schedule.

Disease progression will be considered to be "confirmed" at repeat scan if ANY of the following occur (as assessed by irRECIST):

- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

If repeat scan confirms PD due to any of the scenarios listed above, participants will be discontinued from study therapy.

NOTE: If a participant has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the participant is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor scan, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor scan should continue to be performed following the intervals as outlined in the SoA (Section 2) and be submitted to the iCRO.

Additional details about irRECIST are provided in MSD TIP Sheet for RECIST 1.1 and irRECIST.

Table 13 Scan and Treatment After First Radiologic Evidence of Progressive Disease for Participants Receiving Protocol Treatment

	Clinically Stable		**Clinically Unstable**	
	Scan	**Treatment**	**Scan**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat scan at 4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor scan by site by irRECIST.	Repeat scan at 4 weeks to confirm PD per site investigator discretion only	Discontinue treatment
Repeat tumor scan confirms PD by irRECIST at the local site	No additional scan required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional scan required	Not applicable
Repeat tumor scan shows SD, PR, or CR by irRECIST at the local site	Continue regularly scheduled scan every 9 weeks during neoadjuvant phase and every 12 weeks during adjuvant phase	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled scan every 9 weeks during neoadjuvant phase and every 12 weeks during adjuvant phase	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor scan should occur according to the regular scan schedule

CR=complete response; irRECIST=immune-related response evaluation criteria in solid tumors; PD=progressive disease; PR=partial response; SD=stable disease.

9.2.2 Surgery

Within 3 to 9 weeks following Cycle 3 Day 1 of the neoadjuvant treatment phase or early discontinuation of neoadjuvant treatment, participants will undergo surgery. The standard surgical procedure for this study will be a D2 or D1+ gastrectomy (refer to the Surgical Brochure for details).

Adjuvant treatment will begin within 4 to 10 weeks post-surgery and will not occur unless participants are adequately recovered to restart chemotherapy. If additional recovery time is required, this may be discussed with the Sponsor using a SCF. This is standard practice for the use of peri-operative chemotherapy in patients after gastrectomy or esophagogastrectomy. Details regarding date of surgery, type of surgery, tumor resectability, tumor margins, AEs occurring during the surgical period, etc. will be recorded in the appropriate eCRF. Detailed pathological staging and assessment of surgical margins will be performed by the local pathologist on all the tissues removed during the surgery and recorded in the appropriate eCRF.

9.2.2.1 Pathological Evaluation of Surgically Resected Tumor Tissue

The specimen submitted to the local pathologist must include an entire surgically resected lesion or scar tissue and all resected lymph nodes as per guidelines provided in the Surgical Brochure. If gross viable tumor is present, a minimum of 5 sections of the tumor in the mass lesion should be evaluated. In order to assess the esophagogastrectomy resection, a photograph with the gross lesion must be included. A pathological complete response is defined as 100% fibrosis or fibroinflammation within an entire gross lesion without microscopic evidence of carcinoma, and no positive lymph nodes. The grading of pathologic response will follow the Mandard scale [Mandard, A. M., et al 1994].

The tumor response will be graded from 1 to 5 as follows:

Grade 1: complete regression/fibrosis with no evidence of tumor cells (100% treatment response)

Grade 2: fibrosis with scattered tumor cells (>90% treatment response with <10% viable residual tumor)

Grade 3: fibrosis and tumor cells with a dominance of fibrosis (>75% treatment response with <25% viable residual tumor)

Grade 4: fibrosis and tumor cells with a dominance of tumor cells (<50% treatment response with >50% viable residual tumor)

Grade 5: tumor without evidence of regression (<10% treatment response with >90% viable residual tumor)

9.2.3 Pathological Complete Response

pathCR is defined as having no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes. The primary evaluation of pathCR will be conducted by the local pathologists. All the samples that local pathologists consider as pathCR will be sent to the central laboratory and will be confirmed by central pathologists microscopically. The central pathologist's assessment will overrule the local pathologist's assessment in terms of pathCR if they are different. The samples that local pathologists consider as non-pathCR will not be sent to central laboratory.

In all cases, the site pathologists interpreting surgical specimens for assessment of pathCR will be blinded to treatment assignment. The site pathologists will complete a form from the pathCR vendor that includes information about the operative procedure and surgical margins. A photograph or diagram or radiograph of the entire surgically resected specimen will also be submitted. The guidelines for submission of specimens to the central reviewer will be provided in the Procedures manual.

For participants who do not achieve a pathCR, a tumor tissue sample should be collected and submitted to the designated central laboratory for translational research as specified in Section 5.4.1.4 – Planned Exploratory Biomarker Research. Any leftover tissue will be

archived for future biomedical research (FBR) if the participant has signed the optional

CCI

[redacted]

CCI

[redacted]

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

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

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 180 days following the last dose of chemotherapy or through 120 days following the last dose of pembrolizumab, whichever is greater;

or through 30 days following cessation of study treatment if the participant initiates new anticancer therapy, must be reported by the investigator.

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

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

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 14.

Participants Who Enter the Separate Extension Study:

From the time of treatment allocation/randomization in this study through the signing of the informed consent to the extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (ie, the parent study). Laboratory values that meet criteria for reporting as AEs performed during the parent study will be collected in the parent study.

Note: Once consented to the extension study, AEs and other reportable events meeting the criteria of the extension study, including those considered related to study intervention, will be collected in the extension study.

Table 14 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event		**Reporting Time Period:** **Consent to Randomization/ Allocation**	**Reporting Time Period:** **Randomization/ Allocation through Protocol-Specified Follow-up Period**	**Reporting Time Period:** **After the Protocol Specified Follow-up Period**		**Timeframe to Report Event and Follow-up Information to SPONSOR:**
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required		Per data entry guidelines

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:
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

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

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

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

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

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

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Appendix 4.

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.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously

reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

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

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.

9.3.7 Events of Clinical Interest (ECI)

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

Events of clinical interest for this study include:

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

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

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

9.4 Treatment of Overdose

For the study medications (other than pembrolizumab), an overdose will be defined as any dose ≥20% of the prescribed dose per cycle. The treatment of an overdose of the study medications (other than pembrolizumab) should follow the prescribed information in the approved product labels or local guidelines.

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab of 1000 mg or greater (≥5 times the indicated dose). No specific

information is available on the treatment of overdose of pembrolizumab. In the event of overdose, should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below.

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

9.5.1 Physical Examinations

9.5.1.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the Screening period. A complete physical examination will be conducted as per institutional standard. Height and weight will also be measured and recorded; height will be measured at Visit 1 only.

Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in the SoA (Section 2). After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

9.5.1.2 Directed Physical Exam

For cycles that do not require a full physical exam as defined in the SoA (Section 2), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study treatment. A brief directed physical examination will be conducted as per institutional standard. New clinically significant abnormal findings should be recorded as AEs.

9.5.2 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study treatment and during the follow-up period as specified in the SoA (Section 2).

9.5.3 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

9.5.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Section 12.5, Appendix 5) at screening, prior to dosing on Day 1 of each treatment cycle and at discontinuation of study treatment, as specified in the SoA (Section 2).

9.5.5 Clinical Safety Laboratory Assessments

Refer to Appendix 6 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

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

- All protocol-required laboratory assessments, as defined in Appendix 6, must be conducted in accordance with the laboratory manual and the SoA.

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

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

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 pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Procedures Manual. Refer to the SoA (Section 2) for the timing of laboratory assessments.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 6.

All laboratory tests will be performed by local laboratories on the days and cycles indicated in the SoA (Section 2). Prior to the first dose of study treatment, screening laboratory tests must be performed within 10 days. After neoadjuvant Cycle 1, pre-dose laboratory safety tests can be collected up to 72 hours prior to dosing unless otherwise noted on the SoA (Section 2).

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of study treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within the normal range.

9.5.6 Pregnancy Test

Pregnancy testing ([urine or serum] as required by local regulations) should be conducted prior to every cycle and at the end of relevant systemic exposure for all arms. Pregnancy testing ([urine or serum] as required by local regulations) should be conducted according to Section 2 (SoA) and at the end of relevant systemic exposure for all arms.

- Pregnancy testing requirements for study inclusion are described in Section 6.1.

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

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

- 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.

9.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

9.7 Pharmacodynamics

There will be no blood collection for anti-pembrolizumab antibody detection. Collection of samples for biomarker analyses is described in Section 9.8.

9.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants in this study as specified in the SoA. Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the laboratory manual.

- Blood for genetic analysis
- Blood for RNA analyses
- Blood for serum biomarker analyses

- Blood for circulating tumor DNA (ctDNA)
- Archived or newly obtained tissue collection for biomarker testing

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

9.8.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual.

Samples are to 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 provides documented informed consent for FBR.

9.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- DNA for future research
- Leftover serum from biomarker analyses
- Leftover RNA
- Leftover plasma from ctDNA
- Leftover tumor tissue

9.10 Visit Requirements

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

9.10.1 Screening

Prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1 and Section 6.2. Tumor staging prior to enrollment will include Lauren histological classification. Visit requirements and screening phase windows are outlined in the SoA (Section 2). Screening procedures may be repeated.

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

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

9.10.2 Treatment Period Visit

Visit requirements are outlined in the SoA (Section 2). Specific procedure-related details are provided in Section 9. Unless otherwise specified, assessments/procedures are to be performed prior to administration of study treatment. Unless otherwise specified, the window for each visit is ± 3 days.

9.10.3 Post-treatment Follow-up

9.10.3.1 Safety Follow-up Visit

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

9.10.3.2 Efficacy Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression/recurrence will move into Efficacy Follow-up and should be assessed every 12 weeks (72 ±7 days) by scan until disease progression/recurrence to monitor disease status. Participants should remain on the same scan schedule used while on treatment. For participants that have had surgery, scans should be performed every 12 weeks (±7 days) until 2 years after the date of the post-surgery baseline scan, when the scan schedule will be reduced to every 24 weeks (±7 days). For participants that do not have surgery, scans should be performed every 12 weeks (±7 days) until 2 years after the date of the post-neoadjuvant treatment scan, when the scan schedule will be reduced to every 24 weeks (±7 days) (See Section 9.2.1.3 for additional information). Every effort should be made to collect information regarding disease status until disease progression/recurrence, the start of new anti-cancer therapy, withdrawal of consent, pregnancy, or end of study, whichever occurs first. Information regarding post-study anticancer treatment will be collected if new treatment is initiated. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Participants who complete all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

9.10.3.3 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 and who will not enter the Efficacy Follow-up Phase, 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 the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

9.10.4 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 prior to but not limited to: an external DMC review, interim analysis (IA), and/or final analysis (FA). 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).

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

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

10.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 10.2 through 10.12.

Study Design Overview	A Phase III, Randomized, Double-blind Clinical Trial of Pembrolizumab (MK-3475) plus Chemotherapy (XP or FP) versus Placebo plus Chemotherapy (XP or FP) as Neoadjuvant/Adjuvant Treatment for Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma (KEYNOTE-585).
Treatment Assignment	Main study (XP/FP): Approximately 800 participants will be randomized in the main study in a 1:1 ratio to receive pembrolizumab (MK-3475) plus chemotherapy (XP/FP) or placebo plus chemotherapy (XP/FP). The main study (XP/FP) is double-blinded. FLOT Cohort: Approximately 200 participants will be randomized in a 1:1 ratio to receive pembrolizumab plus FLOT or placebo plus FLOT. The FLOT Cohort is double blinded. Stratification factors are: 1) Geographic regions: (Asia versus Non-Asia), 2) Tumor staging: II versus III versus IVa, and 3) Backbone chemotherapy XP/FP versus FLOT.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	Main study (XP/FP): • Event-free Survival (EFS) assessed by investigators • Rate of Pathological Complete Response (pathCR) • Overall Survival (OS) FLOT Cohort: • AEs; Study treatment discontinuations due to AEs
Secondary Endpoints	Main study (XP/FP): • Disease-free Survival (DFS) assessed by investigators • AEs; Study treatment discontinuations due to AEs Main study (XP/FP) and FLOT Cohort Combined: • Overall Survival (OS) • Event-free Survival (EFS) assessed by investigators • AEs; Study treatment discontinuations due to AEs
Statistical Methods for Key Efficacy Analyses	The primary hypothesis for EFS and OS will be evaluated by comparing pembrolizumab (MK-3475) plus chemotherapy (XP/FP) to placebo plus chemotherapy (XP/FP) using a stratified log-rank test. Estimation of the hazard ratio will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. Treatment comparison of the pathCR rates will be performed using the stratified Miettinen and Nurminen method in the Main Study (XP/FP). Same methods will be used for the analysis of OS and EFS in the Main Study (XP/FP) and the FLOT Cohort combined as secondary hypotheses too.

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. and Nurminen, M. 1985].
Interim Analysis (IA)	CCI Results will be reviewed by an external DMC. Details are provided in Section 10.7. CCI
Multiplicity	The overall type I error over the primary and secondary endpoints (OS, EFS and pathCR rate) is strongly controlled at 2.5% (one-sided), CCI By using the graphical approach of Mauer and Bretz [Maurer, W. and Bretz, F. 2013], if one hypothesis is rejected, the alpha will be shifted to other hypotheses.

Sample Size and Power	The planned sample size is approximately 800 participants in the Main Study (XP/FP), and approximately 200 in the FLOT Cohort. CCI [redacted]

10.2 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 or scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

Planned efficacy interim analyses are described in Section 10.7. Blinding to treatment assignment will be maintained at all investigational sites.

Treatment-level results of the interim analysis will be provided by the unblinded external statistician to the external DMC, which will review the safety and/or efficacy data. Limited additional Sponsor personnel may be unblinded to the treatment level results of the interim analysis (analyses), if required, in order to act on the recommendations of the DMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented in the DMC charter (see Appendix 1).

The DMC will serve as the primary reviewer of the interim analyses and will make recommendations for discontinuation of the study or modification to an executive oversight committee of the Sponsor. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the DMC Charter (see Appendix 1).

Treatment-level results (only safety data) from the FLOT Safety Cohort will be provided by the unblinded external statistician to the siDMC, which will review the data to determine if the FLOT regimen may be incorporated as one of the standard of care chemotherapy backbones in the main study. As above, limited additional Sponsor personnel may be unblinded to the treatment-level results of these analyses if required, in order to act on the recommendations of the siDMC. The extent to which individuals are unblinded with respect to results of these analyses will be documented. Further details on the processes by which recommendations and decisions are reached and communicated will be documented in the siDMC charter (see Appendix 1).

As of Amendment 06, the FLOT Safety Cohort will be expanded to 200 participants to further characterize the safety profile of the combination of FLOT with pembrolizumab and will be designated the FLOT Cohort. Future interim analyses of the FLOT Cohort data will be monitored by the external DMC. As above, limited additional Sponsor personnel may be unblinded to the treatment level results of the interim analysis (analyses), if required, in order to act on the recommendations of the DMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented in the DMC charter (see Appendix 1).

Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.

10.4 Analysis Endpoints

10.4.1 Efficacy Endpoints

Primary

- Event-free survival (EFS) based on RECIST 1.1 as assessed by the investigator.

  EFS is defined as the time from randomization to the first of the following events:

  - Radiographic disease progression per RECIST 1.1
  - Local or distant recurrence as assessed by CT scan or biopsy if indicated (for participants who are disease free after surgery)
  - Clinical progression as evidenced by peritoneal carcinomatosis confirmed by pre-operative laparoscopy or laparotomy (for participants who are confirmed to be free of peritoneal involvement by laparoscopy at screening)
  - Death due to any cause

  A second primary malignancy is not considered as an EFS event.

  Radiographic PD during the neoadjuvant phase that does not preclude successful surgery (ie, disease free after surgery) is not considered as an EFS event.

  For participants with documented peritoneal carcinomatosis found prior to surgery (as evidenced by pre-operative laparoscopy or laparotomy) but without radiographic PD during the neoadjuvant phase and do not undergo screening laparoscopy, EFS data will be censored as of the time of the pre-operative laparoscopy or laparotomy. See Section 10.6.1.1 for the definition of censoring.

- Pathological Complete Response (pathCR) Rate: pathCR rate is defined as the proportion of participants having pathCR. Pathologic complete response (pathCR) is defined as no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes.

- Overall survival (OS) is defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis will be censored at the date of last known alive.

Secondary

- Disease-free survival (DFS) based on RECIST 1.1 as assessed by investigator. DFS is defined as the time from post-surgery baseline scan until the first occurrence of:
  - Local or distant recurrence;
  - Death from any cause.

10.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, AEs leading to discontinuation, SAEs, fatal AEs, physical examination, vital signs, ECOG performance status, and lab values. Furthermore, specific events will be collected and designated as ECIs as described in Section 9.3.7.

10.4.3 Patient-Reported Outcome Endpoints

Health-related QoL assessments using the EORTC QLQ-C30 and EORTC QLQ-STO22; utility assessments using EQ-5D 5L.

10.5 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.

10.5.1 Efficacy Analysis Populations

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

DFS analysis population will be those participants who are disease free at the post-surgery baseline scan.

Details on the approach to handling missing data are provided in Section 10.6, Statistical Methods.

10.5.2 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety data. The APaT population consists of all randomized participants who received study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study medication for 1 cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

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

Details on the approach to handling missing data for safety analyses are provided in Section 10.6 Statistical Methods.

10.5.3 Patient-reported Outcome Analysis Populations

Patient-reported Outcome analyses are based on the PRO Full Analysis Set (FAS) population, defined as participants who have at least one PRO assessment available and have received at least one dose of study treatment.

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

In this section, for the stratified analyses, small strata may be collapsed. Additional details will be provided in the sSAP.

10.6.1.1 Event-free Survival (EFS)

The non-parametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The treatment difference in EFS will be assessed by the stratified log-rank test and the p-value will be provided. 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 for the treatment covariate will be reported. The stratification factors used for randomization (see Section 7.3.1) will be applied to both the stratified log-rank test and the stratified Cox model. In case of small strata, the stratification factors will be combined in stratified analysis and details will be provided in the sSAP.

For the primary analysis of EFS as assessed by investigators, the true date of disease progression/recurrence will be approximated by the date of the first assessment at which event is objectively documented, regardless of discontinuation of study drug, missed study visits, or initiation of new anti-cancer therapy. Participants who do not experience an event at the time of analysis will be censored at the last disease assessment. As a sensitivity analysis, this same approach will also be applied to analysis of EFS as assessed by BICR. Sensitivity analyses may be conducted using different censoring rules and will be documented in the sSAP.

10.6.1.2 Pathological Complete Response (pathCR) Rate

The stratified Miettinen and Nurminen's method with strata weighted by sample size will be used for the comparison of pathCR rates between pembrolizumab with chemotherapy (XP/FP) and chemotherapy alone. The stratification factors used for randomization (see Section 7.3.1) will be applied. In case of small strata, the stratification factors will be combined in stratified analysis and details will be provided in the sSAP.

10.6.1.3 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference measured by the hazard ratio (HR). The HR and its 95% CI from the Cox model for the treatment covariate will be reported. The stratification factors used for randomization (See Section 7.3.1) will be applied to both the stratified log-rank test and the stratified Cox model. In case of small strata, stratification factors will be combined to ensure a sufficient number of events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock for any efficacy interim or final analysis based on a blinded review of event counts by stratum. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

10.6.1.4 Analysis Strategy for Key Efficacy Variables

Table 15 the primary analysis approach for key efficacy endpoints.

Table 15 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
EFS	Test: stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis (More details provided in the sSAP)
pathCR rate	Stratified M&N method	ITT*	Participants with relevant data missing are considered non-responders
OS	Test: stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date

EFS=event-free survival; ITT=intention to treat; OS=overall survival

†Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (See Section 7.3.1 – Stratification) will be applied to the analysis model. In case of small strata, the stratification factors will be combined in stratified analysis and details will be provided in the sSAP.

*For IA1 in Section 10.7 pathCR rate analysis, participants randomized at least 6 months before the data cutoff will be included.

10.6.1.5 Disease-free Survival (DFS)

The non-parametric Kaplan-Meier method will be used to estimate the DFS curve for each treatment group.

10.6.2 Statistical Methods for Safety Analyses

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

Adverse Events

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped system organ class. AEs will be graded by the investigator according to the CTCAE, version 4.0.

The analysis of safety results will follow a tiered approach as shown in Table 16. The tiers differ with respect to the analyses that will be performed. 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. Based on the safety knowledge accumulated across the program to date, there are no events that warrant consideration for Tier 1.

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥2% of participants in 1 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 as a formal method for assessing the statistical significance of the between-group differences.

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 16 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	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 (≥2% of participants in one of the treatment groups)		X	X
Tier 3	Any AE			X
	Any Serious AE			X
	Any Grade 3-5 AE			X
	Any Drug related AE			X
	Any Serious and Drug related AE			X
	Any Grad 3-5 and Drug related AE			X
	Discontinuation due to AE			X
	Any AE leading to death			X
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)			X
	Change from baseline results (laboratory test toxicity grade, vital signs)			X

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

10.6.3 Statistical Methods for Patient-reported Outcome Analyses

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

10.6.4 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

10.7 Interim Analyses

Both efficacy and safety results will be reviewed by an external DMC. The timing of safety reviews will be documented in the DMC Charter based on consultation with external DMC members. CCI [redacted]. Details of the multiplicity strategy for group sequential design are provided in Section 10.8.

CCI

10.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the primary and secondary hypotheses including EFS in the Main Study (XP/FP) (H1), pathCR rate in the Main Study (XP/FP) (H2), OS in the Main Study (XP/FP) (H3), OS in Main Study (XP/FP) and FLOT Cohort combined (H4), and EFS in the Main Study (XP/FP) and FLOT Cohort combined (H5), respectively. The graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] will be taken to strongly control the overall Type I error rate for testing of multiple endpoints at 2.5% 1-sided. See Figure 3 for the multiplicity strategy diagram of the study. The weights for re-allocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses. For EFS and OS hypotheses, the Lan-DeMets O'Brien-Fleming approximation alpha spending function is used to control multiplicity for the interim analyses and final analysis.

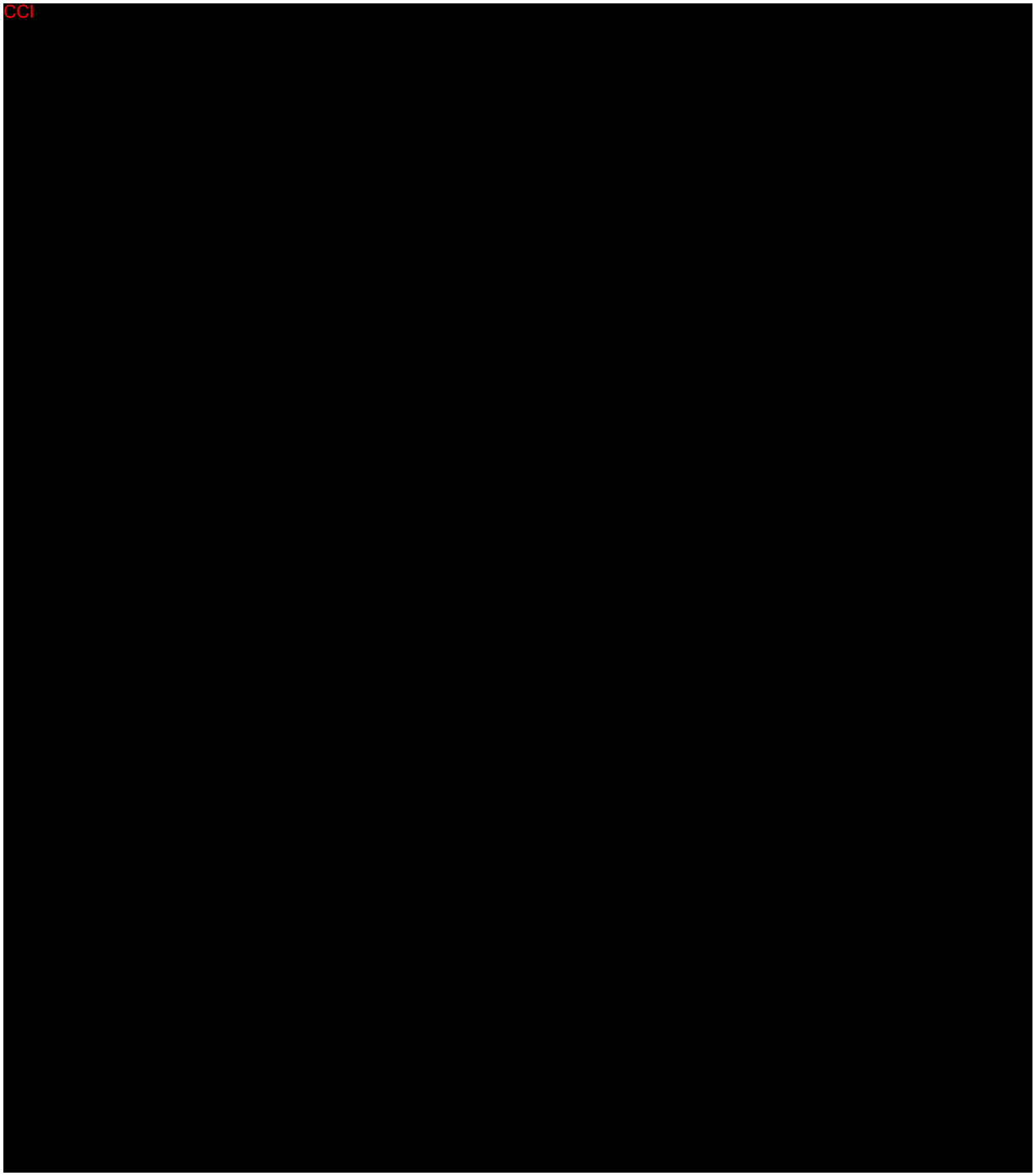
CCI

CCI [redacted]

To account for any multiplicity concerns raised by the DMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for OS will be pre-specified in the sSAP. This analysis will be CCI [redacted]

10.8.1 Event-free Survival

Figure 3 shows that the EFS hypothesis in the Main Study (XP/FP) (H1) CCI [redacted]


CCI

CCI

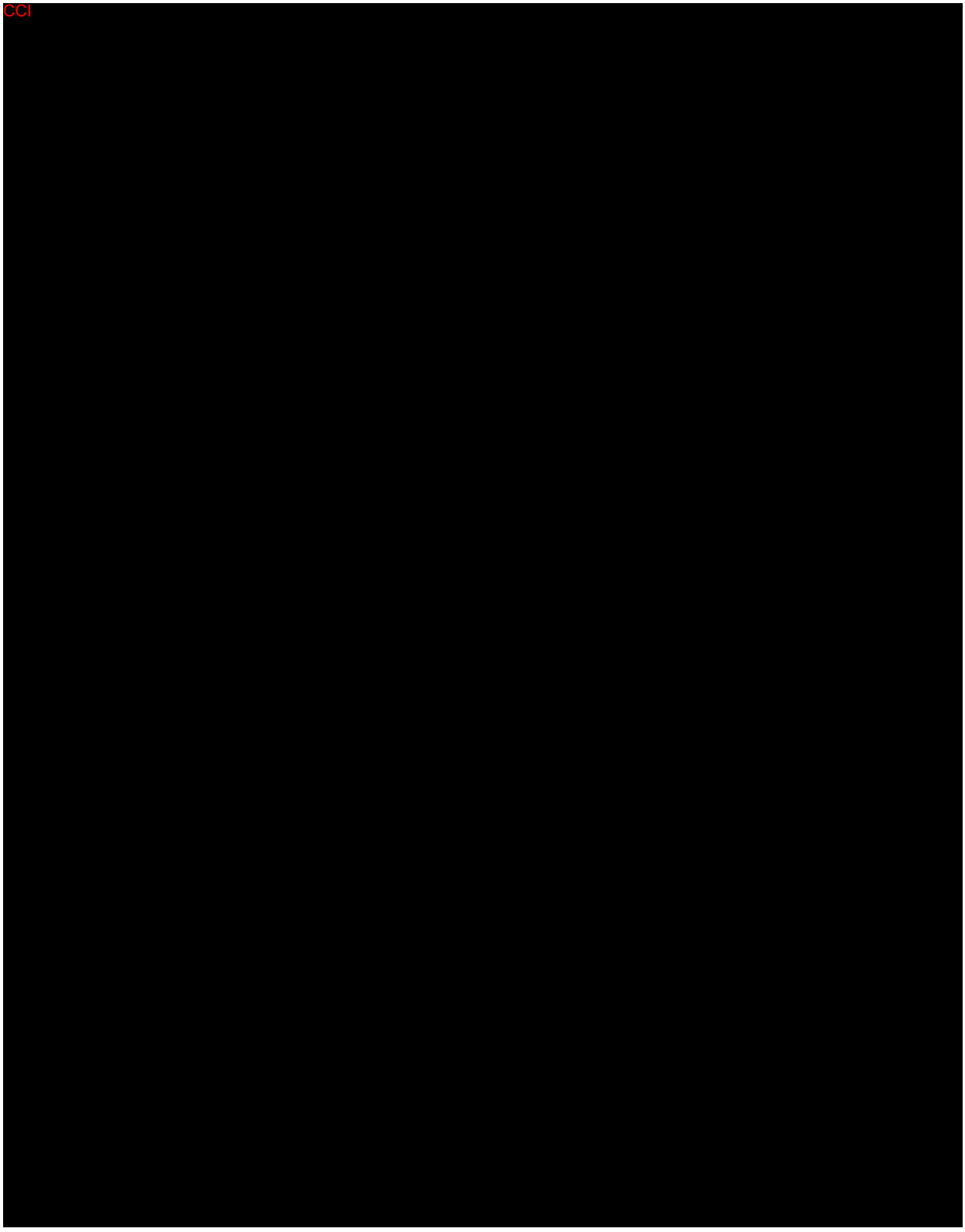
[redacted]

10.8.2 Overall Survival

Figure 3 shows that the CCI

[redacted]

CCI



CCI

[redacted]

10.8.3 Pathological Complete Response

CCI

[redacted]

10.9 Sample Size and Power Calculations

The main study (XP/FP) will randomize approximately 800 participants in a 1:1 ratio between the 2 groups while the FLOT Cohort will randomize approximate 200 participants in a 1:1 ratio as well.

Main Study (XP/FP)

PathCR rate:

The pathCR rate analysis will be performed at IA1. Participants randomized in the Main Study (XP/FP) at least 6 months before the IA1 data cutoff will be included in pathCR rate analysis.

It is estimated that ~800 participants in the Main Study will be included.

CCI [redacted]

EFS:

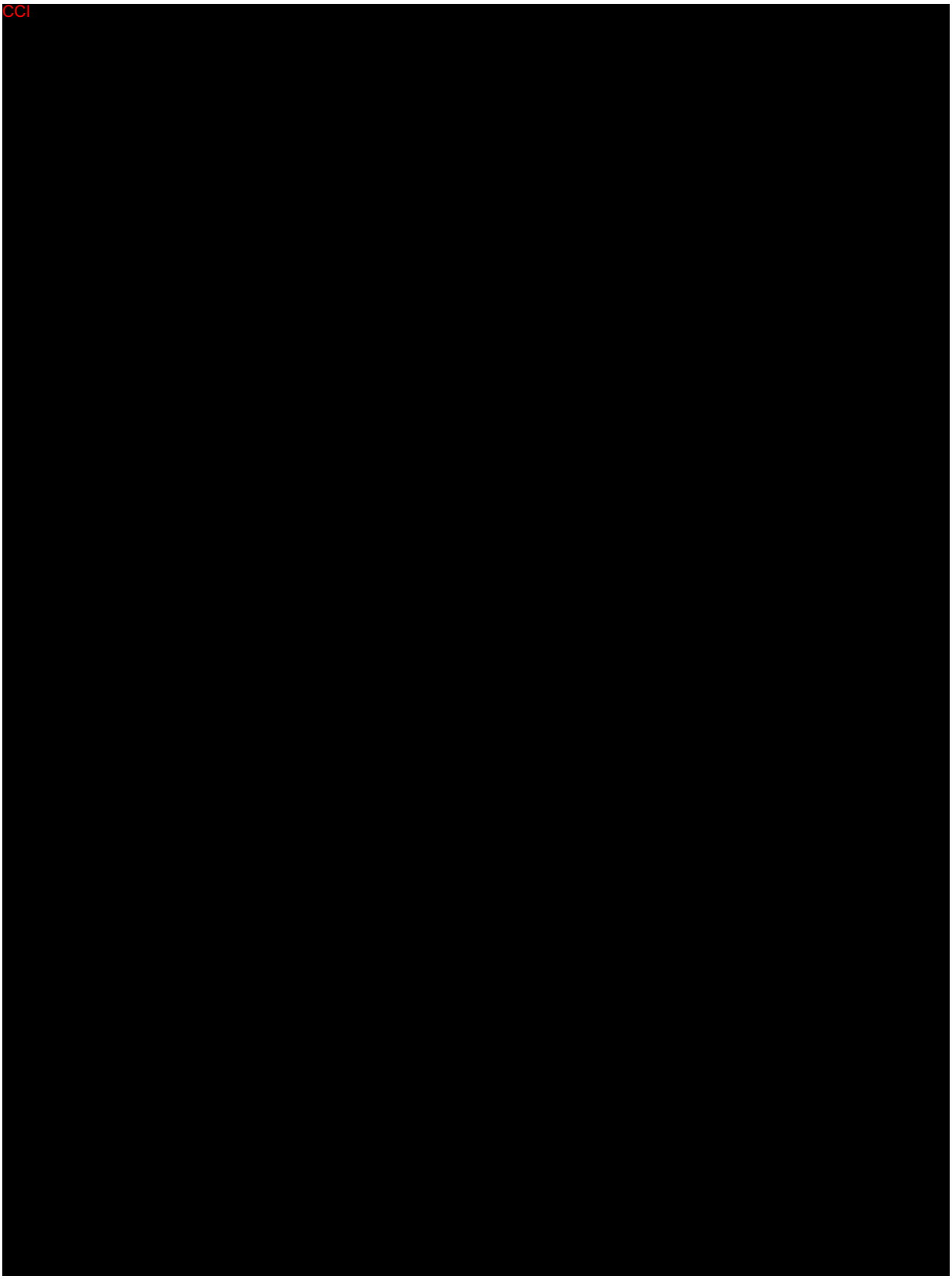
The final analysis of EFS CCI [redacted]

[redacted]

OS:

If EFS in the Main Study (XP/FP) (H1) is rejected, CCI [redacted]

CCI



CCI

[redacted]

All sample size and power calculations were performed using the R software package gsDesign.

10.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for OS and EFS (with a nominal 95% CI) will be estimated and plotted within each category of the following classification variables:

- Geographic region (Asia versus Non-Asia)
- Tumor staging (II versus III versus IVa)
- Tumor location (Stomach versus GEJ)
- PD-L1 (+ versus -)
- Age category (<65 versus ≥65 years)
- Gender (Male versus Female)
- Race (Asian versus Non-Asian)
- Backbone therapy (FP versus XP [versus FLOT*])

Subgroup analyses will be performed on the Main Study (XP/FP) as well as on the Main Study (XP/FP) and FLOT Cohort combined. The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot.

*Category of FLOT for the subgroup variable of backbone therapy is only applicable to the subgroup analyses for the Main Study (XP/FP) and FLOT Cohort combined.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

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

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12. Appendices

12.1 Appendix 1: Study Governance Considerations

Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, 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 and shall respect the data protection rights of

all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors using a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (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.

Financial Disclosure

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

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

Data Protection

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

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

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

Confidentiality of Data

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

Confidentiality of Participant Records

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

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

Confidentiality of IRB/IEC Information

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

Committees Structure

Scientific Advisory Committee

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

Study Steering Committee

This study will be conducted in consultation with a Study Steering Committee which will provide guidance on the operational aspects of the study as needed. The Study Steering Committee comprises:

- Sponsor personnel
- Investigators participating in the study
- Consulting therapeutic-area experts and clinical trialists

    1. Surgical oncologists will provide guidance for standardization of the surgical procedure to be used for the treatment of participants on this study, in the form of a Surgical Brochure that will accompany the protocol for implementation at all participating sites globally

2. Pathologists will provide guidance for development of a tumor regression grading system to evaluate treatment responses and standardized guidelines for the diagnosis of pathCR

3. Medical oncologists will provide guidance on the standardization of the therapeutic regimen and other aspects of neoadjuvant and adjuvant trials

Executive Oversight Committee

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

Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (see Section 10.7 - Interim Analyses) and recommend to the EOC if 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.

To supplement the routine monitoring outlined in this protocol, a separate standing internal Data Monitoring Committee (siDMC) will monitor the safety only data from the FLOT Safety Cohort. The siDMC comprises members of Sponsor Senior Management, none of whom are directly associated with the conduct of this trial.

As of Amendment 06, the FLOT Safety Cohort will be expanded and designated the FLOT Cohort. Future interim analyses of the FLOT Cohort will be monitored by the external DMC.

The siDMC will monitor the FLOT Safety Cohort for evidence of adverse effects of trial treatment as described in the detailed monitoring guidelines. The siDMC will determine whether the FLOT + pembrolizumab/placebo regimen should continue according to the protocol and if FLOT can be added as a chemotherapy backbone choice. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the trial.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

Publication Policy

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

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

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

Compliance with Study Registration and Results Posting Requirements

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

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

Compliance with Law, Audit and Debarment

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

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

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

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

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

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

Data Quality Assurance

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

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

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

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

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

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

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

Records and documents including 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.

Source Documents

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

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

Study and Site Closure

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

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

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 9.9 – Future Biomedical Research Sample Collection will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in 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 electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

At the clinical study site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally

identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in 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@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

13. References

1. National Cancer Institute: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; Available from: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Congenital or acquired condition that prevents childbearing
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - Bilateral tubal ligation/occlusion at least 6 weeks prior to screening.

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.

Contraception Requirements

Male Participants

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

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

Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a 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 reproductive potential must agree to consistent and correct use of a highly effective method of contraception as described in Table 22 while receiving study drug and through 180 days after the last dose of chemotherapy; or through 120 days after the last dose of pembrolizumab, whichever is last.

Table 22 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).

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

Definition of AE

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

Events <u>Meeting</u> the AE Definition
● Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. ● Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. ● New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. ● Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. ● Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. ● For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." ● Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

Events NOT Meeting the AE Definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to section 9.3.5 for protocol specific exceptions

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

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

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

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Recording AE and SAE

AE and SAE Recording
● When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. ● The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination. ● It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page. ● There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor. ● The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity

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

Assessment of Causality

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

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

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

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

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor’s product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse event to the single agent.

Follow-up of AE and SAE

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

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

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

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

12.5 Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE 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 selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

[Oken, M. M., et al 1982]

http://ecog-acrin.org/resources/ecog-performance-status

12.6 Appendix 6: Clinical Laboratory Tests

- The tests detailed in Table 23 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 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 23 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit		WBC Count with Differential [1] Neutrophils [1] Lymphocytes [1]	
Chemistry	Blood Urea Nitrogen (BUN) or Urea	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total Bilirubin (and Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Carbon dioxide (CO_2 or Bicarbonate) [2]	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline Phosphatase	Lactate dehydrogenase
Routine Urinalysis	• Specific gravity • Glucose, protein, blood, by dipstick • Microscopic examination (if blood or protein is clinically significant)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for women of childbearing potential) [3] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody), anti-HBc (total and IgM), anti-HBe, if applicable [4] • PT/INR • aPTT/PTT • Total T3 or free T3, FT4, and TSH [5]			

aPTT=activated partial thrombin time; FT4=free thyroxine; anti-HBe=anti-hepatitis B envelope; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; IgM=gamma M immunoglobulin; INR=International Normalized Ratio; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cells; T3=triiodothyronine; TSH=thyroid stimulating hormone (thyrotropin); WBC=white blood cells.

NOTES :

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

[2] If this test is not done as part of local standard of care, this test does not need to be performed.

[3] For women of reproductive potential, a pregnancy test must be performed within 72 hours prior to administration of study treatment on the days and cycles indicated in the SoA (Section 2), and 30 days post-treatment discontinuation. If a urine test is positive or not evaluable, a serum test will be required.

[4] No testing for HIV, hepatitis B, or Hepatitis C is required unless mandated by local health authority.

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

12.7 Appendix 7: Technical Note for the Statistical Model

12.7.1 Poisson Mixture Model

The Poisson mixture model is applied to account for the failure rates decreasing over time in the study which is a mixture of participants suffering disease recurrence and others who have excellent long-term results. The survival function [de Castro, M., et al 2010] as a function of time t for a control group (c) is:

$$S(t)=e^{-\theta(1-e^{\wedge}(-\lambda t))},$$

where θ = *-log(Cure_Rate)*, λ is a constant hazard rate, and $t \geq 0$.

The parameters in this Poisson mixture model on the control group in the Main Study (XP/FP) are based on published literature MAGIC study [Cunningham, D., et al 2006] and ACTS-GC study [Sasako, M., et al 2011]. The MAGIC study had only Western patients and the ACTS-GC study had only Asian participants. Since KEYNOTE 585 is a global study, the parameters were chosen to be in the range of the MAGIC and ACTS-GC studies. It is assumed that ~ 40% participants could achieve excellent long-term results (ie, the cure rate is 40%), median EFS of 30 months, and median OS of 42 months on the control group in KEYNOTE 585.

Figure 4 and Figure 5 show the shape of the survival curves of EFS and OS for Poisson Mixture Model and exponential distribution model with the same assumption of the median on the control group in the Main Study (XP/FP).

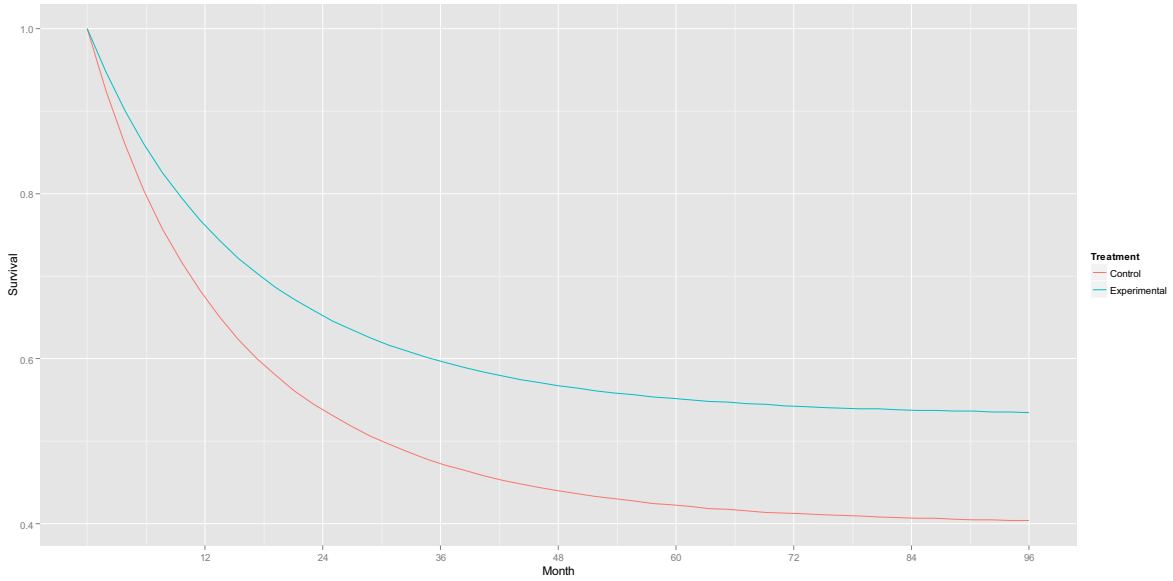

Figure 4 Survival Curves of EFS Under Poisson Mixture Model and Exponential Distribution Model

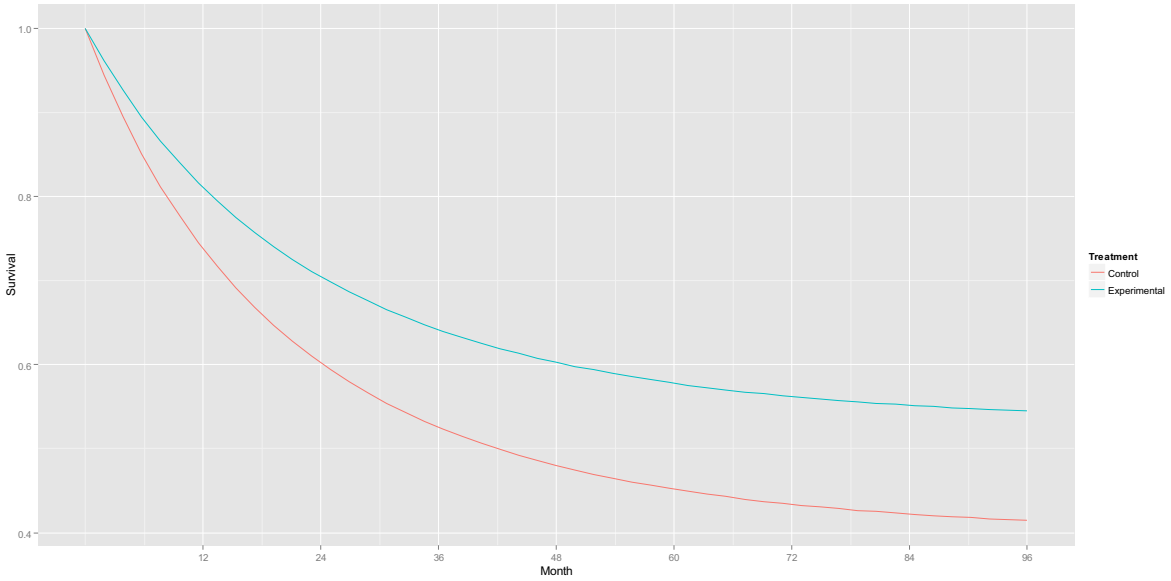

Figure 5 Survival Curves of OS Under Poisson Mixture Model and Exponential Distribution Model

Similarly, Poisson mixture model has been assumed for the control group in the FLOT Cohort as well, with median EFS of 30 months and median OS of 50 months [Fuchs, C. S., et al 2019].

12.7.2 Approximated Overall HR for the Main Study (XP/FP) and FLOT Cohort Combined

Assume the endpoint of interest (either EFS or OS) follows a Poisson Mixture distribution with different cure rate:

denote XP/FP cure rate as $e^{-\theta}$ and FLOT cure rate as $e^{-\theta\rho}$,

and a common constant hazard rate (λ) in each of the 4 populations: the XP/FP control group, FLOT control group, XP/FP experiment group, FLOT experiment group.

Further assume the hazard ratio in the Main Study (XP/FP) and the FLOT Cohort can be different and denote by $HR_F=0.78$ and $HR_{NF}=0.72$ for EFS and $HR_F=0.80$ and $HR_{NF}=0.74$ for OS, respectively. Then the survival function for each of the cohort are with the form:

	XP/FP Control Group	FLOT Control Group	XP/FP Experiment Group	FLOT Experiment Group
Survival Function	$e^{-\theta(1-e^{\wedge}(-\lambda t))}$	$e^{-\theta\rho(1-e^{\wedge}(-\lambda t))}$	$e^{-\theta*HR_{NF}*(1-e^{\wedge}(-\lambda t))}$	$e^{-\theta*\rho*HR_{F}*(1-e^{\wedge}(-\lambda t))}$

Above survival functions for control groups can be used to calculate the parameters (θ,λ,ρ) given control group information including cure rate of the main study (XP/FP) and the control medians (either median EFS or median OS) from both the Main Study (XP/FP) and the FLOT Cohort. The EFS or OS survival rate based on each of the above survival functions can be explicitly calculated with assumed hazard ratios from both the Main Study (XP/FP) and the FLOT Cohort as well as the calculated parameters (θ,λ,ρ).

Let the percentage of participants in FLOT Cohort compared with XP/FP and FLOT combined be P (P=200/100=20%). Then the control group survival function can be written as

$$Pe^{-\theta\rho(1-e^{\wedge}(-\lambda t))} + (1-P)e^{-\theta(1-e^{\wedge}(-\lambda t))} \quad \ldots(\text{Eq.1}),$$

which can be approximated by a Poisson mixture model at a preselected landmark time of t:

$$e^{-\theta v_0 (1-e^{\wedge}(-\lambda t))} \quad \ldots(\text{Eq.2}).$$

Here v_0 is calculated so that the survival rate at time t is the same for the 2 survival functions in Eq. 1. and Eq. 2.

Similarly, the experimental group survival function can be written as

$$Pe^{-\theta*\rho*HR_F*(1-e^{\wedge}(-\lambda t))} + (1-P)e^{-\theta*HR_{NF}*(1-e^{\wedge}(-\lambda t))} \quad \cdots(\text{Eq.3}),$$

which can be approximated by a Poisson mixture model at a preselected landmark time of t:

$$e^{-\theta v_1 (1-e^{\wedge}(-\lambda t))} \quad \ldots(\text{Eq.4}).$$

Here v_1 is calculated so that the survival rate at time t is the same for the 2 survival functions in Eq. 3. and Eq. 4.

Then v_1/v_0 can be considered as an approximated overall HR for sample size/power calculation for the Main Study (XP/FP) and FLOT Cohort combined.

In gastric neoadjuvant/adjuvant trials, 5-year OS rate and 3-year EFS rate provide clinically meaningful information and are often reported in the literature. Thus t=36 months and t=60 months are assumed as the landmark times for the computation of the overall approximated HR in the main study and FLOT Cohort combined for EFS and OS, respectively. The approximated overall HR for the Main Study (XP/FP) and FLOT Cohort Combined was calculated to be 0.75 for OS and 0.73 for EFS.

12.8 Appendix 8: Abbreviations and Trademarks

Abbreviation/Term	Definition
1L	first line
2L	second line
3L	third line
5-FU	5-fluorouracil
ACTS-GC	Adjuvant Chemotherapy Trial of TS1 for Gastric Cancer
AE	adverse event
ALT	alanine aminotransferase
APaT	all participants as treated (population)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
bid	2 times a day
BSA	body surface area
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CLASSIC	Capecitabine and Oxaliplatin Adjuvant Trial in Stomach Cancer
C_{max}	serum maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CrCl	calculated creatinine clearance
CRF	case report form
CRT	chemoradiation therapy
CSR	clinical study report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	serum minimum concentration
DFS	disease-free survival
DL	dose level
DMC	data monitoring committee
DPD	dihydropyrimidine dehydrogenase
DNA	deoxyribonucleic acid
DSS	disease-specific survival
ECF	epirubicin + cisplatin + 5-FU
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
e-CRF	electronic case report form
ECX	epirubicin + cisplatin + capecitabine

Abbreviation/Term	Definition
EFS	event-free survival
EMA	European Medicines Agency
EOC	executive oversight committee
EOF	epirubicin + oxaliplatin + 5-FU
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EORTC QLQ-STO22	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-STO22
EOX	epirubicin + oxaliplatin + capecitabine
ePRO	electronic patient-reported outcome(s)
EQ-5D-5L	EuroQol-5 Dimension Questionnaire
FA	final analysis
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFCD	The Fédération Francophone de Cancérologie Digestive
FLAGS	Phase III trial to compare the oral fluoropyrimidine S1 plus cisplatin versus 5-FU plus cisplatin
FLOT	docetaxel, oxaliplatin, fluorouracil, and leucovorin (calcium folinate)
FNA	fine needle aspirate
FP	cisplatin + 5-fluorouracil
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	Health Related Quality of Life
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	Imaging Contract Research Organization
IEC	independent ethics committee
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL-10	interleukin 10
INR	international normalized ratio

Abbreviation/Term	Definition
irAE	immune-related adverse event
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IRB	institutional review board
IRT	interactive response technology
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
ITT	intention to treat
IV	intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
MAGIC	The Medical Research Council Adjuvant Gastric Infusional Chemotherapy study
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
N/A	not applicable
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
OTC	over-the-counter
pathCR	pathological complete response
PBPK	physiologically-based pharmacokinetic(s)
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
PIN	personal identification number
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PRO	patient-reported outcome(s)
PT	prothrombin time
PS	performance status
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ	Quality of Life Questionnaire
QoL	quality of life
R0	complete surgical resection
R1	microscopic involvement at the margins
R2	evidence of macroscopic residual disease

Abbreviation/Term	Definition
RCC	renal cell cancer
REAL-2	Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RR	response rate
RT	radiation therapy
SAC	scientific advisory committee
SAE	serious adverse event
SCF	Sponsor consultation form
siDMC	standing internal Data Monitoring Committee
SLAB	supplemental lab tests (CRF)
SNP	single nucleotide polymorphism
SoA	Schedule of Activities
SOP	standard operating procedure
SPIRITS	The S 1 Plus cisplatin versus S 1 In RCT In the Treatment for Stomach cancer study
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction(s)
T1DM	Type 1 Diabetes Mellitus
TB	tuberculosis
TEA	Treatment Eligibility Assessment
TSH	thyroid stimulating hormone
WBC	white blood cells
WOCBP	Women of child-bearing potential
XP	cisplatin + capecitabine

12.9 Appendix 9: Country-specific Requirements

12.9.1 France-specific Requirements

For all sites in France, participants with creatinine clearance ≤60 mL/min should not be allowed to participate in this study.

Sites in France will not participate in the FLOT Cohort and will not use the FLOT regimen before authorization by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM).

Section 7.2.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

Pembrolizumab treatments must be suspended in the event of the following adverse events of immunological origin:

- Grade 3 skin or suspected Stevens-Johnson syndrome (SJS)
- Suspected toxic epidermal necrolysis

Pembrolizumab treatments must be discontinued in the event of the following confirmed adverse events of immunological origin:

- Stevens-Johnson syndrome
- Toxic epidermal necrolysis