Official Protocol Title:	A Phase 3, Randomized Study to Evaluate the Efficacy and Safety of Lenvatinib (E7080/MK-7902) plus Pembrolizumab (MK-3475) plus Chemotherapy Compared with Standard of Care Therapy as First-line Intervention in Participants with Advanced/Metastatic Gastroesophageal Adenocarcinoma (LEAP-015)
NCT Number:	NCT04662710
Document Date:	10-Jun-2025

TITLE PAGE

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Protocol Title: A Phase 3, Randomized Study to Evaluate the Efficacy and Safety of Lenvatinib (E7080/MK-7902) plus Pembrolizumab (MK-3475) plus Chemotherapy Compared with Standard of Care Therapy as First-line Intervention in Participants with Advanced/Metastatic Gastroesophageal Adenocarcinoma (LEAP-015)

Protocol Number: 015-08 (E7080-G000-321)

Compound Number: MK-7902

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

The study is part of a collaboration between MSD and Eisai

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	Not applicable
EU CT	2023-504834-23
EudraCT	2020-001990-53
JRCT	2051200127
WHO	U1111-1288-1010
UTN	U1111-1288-1010
IND	140284

Approval Date: 10 June 2025

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 8	10-JUN-2025	This change was made to include an extension study option and remove the option for starting Second Course Treatment Phase. Second Course Treatment Phase is removed due to study close-out activities and transitioning participants to extension study.
Amendment 7	29-JUN-2024	Revisions to align with Regulation (EU) 536/2014.
Amendment 6	11-AUG-2023	CCI [redacted]
Amendment 5	07-OCT-2022	
Amendment 4 – Country-specific	22-DEC-2021	To address request from Peru National Institute of Health related to justification of inclusion of esophageal adenocarcinoma participants.
Amendment 3	29-JUN-2021	To address Health Authority requests and to include updates based on pembrolizumab and lenvatinib template revisions, including to update the pembrolizumab dose modification and toxicity management guidelines for irAEs.
Amendment 2	23-FEB-2021	Update protocol in response to recently presented data from CM649, ATTRACTION-4 and KN590 studies, and make updates in response to Regulatory Authority input. Revise lenvatinib dose in consolidation. Alignment of dose modification table with global program standards.
Amendment 1	03-FEB-2021	Update protocol in response to recently presented data from CM649, ATTRACTION-4 and KN590 studies, and make updates in response to Regulatory Authority input. Revise lenvatinib dose in consolidation.
Original Protocol	11-SEP-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendment:

This change was made to include an extension study option and remove the option for starting Second Course Treatment Phase. Second Course Treatment Phase is removed due to study close-out activities and transitioning participants to extension study.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis	Added text describing the inclusion of an extension study option and removal of Second Course Treatment Phase.	This change was made to include an extension study option and remove the option for starting Second Course Treatment Phase. Second Course Treatment Phase is removed due to study close-out activities and transitioning participants to extension study.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1, Synopsis	Added note about changes to imaging requirements .	To provide new information for performing imaging per local standard of care.
Section 1.2, Schema	Added note that the Second Course Treatment Phase (Figure 3) will no longer be offered.	See rationale for Section 1.1 under primary reason.
	Added note about changes to imaging requirements.	See rationale for Section 1.1 under additional changes.
Section 1.3, Schedule of Activities	Simplified Schedule of Activities (SoA) for ePROs to show only the required. assessments for participants active on treatment.	In accordance with the overall rationale for the amendment, assessments/procedures are simplified.
	Simplified Schedule of Activities (SoA) for blood for RNA analysis to show only the required assessments for participants active on treatment.	See rationale for Section 1.3.
	Simplified Schedule of Activities (SoA) for blood for serum biomarkers to show only the required assessments for participants active on treatment.	See rationale for Section 1.3.
	Simplified Schedule of Activities (SoA) for ctDNA analysis to show only the required assessments for participants active on treatment.	See rationale for Section 1.3.

Section Number and Name	Description of Change	Brief Rationale
	Simplified Schedule of Activities (SoA) for tumor imaging to show only the required assessments for participants active on treatment.	See rationale for Section 1.3.
Section 1.3.5, Second Course (Part 1 and Part 2)	Updated Second Course Treatment Phase.	See rationale for Section 1.1 under the primary reason.
Section 4.1, Overall Design	Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged, and a note has been added regarding the removal of the Second Course Treatment Phase.	See rationale for Section 1.1.under the primary reason.
	Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged, and a note has been added regarding the safety, efficacy, and survival follow-up after discontinuation.	See rationale for Section 1.1 under the primary reason.
	Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged, and a note has been added regarding the inclusion of extension study.	See rationale for Section 1.1 under the primary reason.
	Added note about changes to imaging requirements.	See rationale for Section 1.1. under the additional changes.
Section 4.2.1.3, Patient-reported Outcomes	Added note regarding updates to ePROs.	Removed ePROs assessments at C>18, EOT, and Safety Follow-up.
Section 6, Study Intervention	Added text for reporting requirements of clinical supply complaints and/or temperature excursions.	To align language with new Online Clinical Supply Incident Reporting Form to report clinical supply complaints, site temperature excursions, and dosing past expiry.
Section 6.6.6, Second Course	Option for Second Course Treatment Phase is removed due to study close-out activities and transitioning participants to extension study.	See rationale for Section 1.1 under the primary reason.
Section 8.2.1.2, Tumor Scans During the Study	Added note about changes to imaging requirements.	See rationale for Section 1.1 under the additional changes.
Section 8.2.1.3, End-of-treatment and Follow-up Tumor Scans	Added note about changes to the collection of tumor scans during follow-up.	See rationale for Section 1.1 under the additional changes.
Section 8.2.1.4, Second Course (Retreatment) Tumor Scans	Added note about changes to imaging requirements.	See rationale for Section 1.1 under the additional changes.
Section 8.2.1.5, RECIST 1.1 Assessment of Disease	Added note about changes to imaging requirements.	See rationale for Section 1.1 under the additional changes.
Section 8.2.2.1, Patient-Reported Outcomes	Added note regarding updates to ePROs.	See rationale for Section 4.2.1.3.

Section Number and Name	Description of Change	Brief Rationale
Section 8.4 1, Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events	Added text regarding safety assessments during the extension study.	To align safety assessments with the Amendment 8.
	Table 13: Updated periods and duration for potential DILI events meeting biochemical criteria of Hy's Law.	To maintain continued regulatory reporting compliance in alignment with new Health Authority DILI reporting requirements.
Section 8.4.3, Follow -up of AE, SAE, and other Reportable Safety Event Information	Added potential DILI events meeting biochemical criteria of Hy's Law to list of reportable safety events.	See rationale for Section 8.4 1, DILI reporting.
Section 8.4.7, Events of Clinical Interest	ECI updated to include potential DILI meeting biochemical criteria of Hy's Law, with associated reporting requirements.	See rationale for Section 8.4 1, DILI reporting.
Section 8.11.5.2, Efficacy Follow-up Visit(s)	Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged, and a note has been added regarding changes to imaging requirements.	See rationale for Section 1.1. under the additional changes.
Section 8.11.5.3, Survival Follow-up Contacts	Where deletion of text could cause confusion, due to the design of the study to date, the text has been left unchanged, and a note has been added regarding the survival follow-up.	See rationale for Section 1.1 under the primary reason..
Section 10.3.3, Definition of SAE	Added potential DILI events meeting biochemical criteria of Hy's Law to definition of SAE.	Refer to rationale for Section 8.4.1, DILI reporting.
Section 10.7.2.10, Japan	Country-specific text describing background chemotherapy.	Due to 5-FU shortage, locally sourced 5-FU will be supplied as 1,000 mg/20 mL vials.
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 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized Study to Evaluate the Efficacy and Safety of Lenvatinib (E7080/MK-7902) plus Pembrolizumab (MK-3475) plus Chemotherapy Compared with Standard of Care Therapy as First-line Intervention in Participants with Advanced/Metastatic Gastroesophageal Adenocarcinoma (LEAP-015)

Short Title: Lenvatinib plus Pembrolizumab plus Chemotherapy for the Treatment of Advanced/Metastatic Gastroesophageal Adenocarcinoma

Acronym: LEAP-015

Hypotheses, Objectives, and Endpoints:

Male and female adults, at least 18 years of age with previously untreated, locally advanced unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma will be enrolled, and the following objectives and endpoints will be assessed (there are dual primary endpoints):

Primary Objective	Primary Endpoint
- Objective (Part 1): To evaluate the safety and tolerability of treatment with lenvatinib plus pembrolizumab plus chemotherapy.	- Dose-limiting toxicities, adverse events and study intervention discontinuations due to adverse events.
- Objective (Part 2): To compare the overall survival between treatment groups - Hypothesis (H1): Lenvatinib plus pembrolizumab plus chemotherapy is superior to chemotherapy for OS in participants with programmed cell death ligand 1 combined positive score ≥1. - Hypothesis (H3): Lenvatinib plus pembrolizumab plus chemotherapy is superior to chemotherapy for OS in all participants.	- Overall Survival: The time from randomization to death due to any cause

- Objective (Part 2): To compare the PFS between treatment groups - Hypothesis (H2): Lenvatinib plus pembrolizumab plus chemotherapy is superior to chemotherapy alone for PFS per RECIST 1.1 as assessed by BICR in participants with programmed cell death ligand 1 combined positive score ≥1. - Hypothesis (H4): Lenvatinib plus pembrolizumab plus chemotherapy is superior to chemotherapy for PFS per RECIST 1.1 as assessed by BICR in all participants.	- Progression-free Survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Secondary Objectives	**Secondary Endpoints**
- Objective (Part 2): To compare ORR between treatment groups. - Hypothesis (H5): Lenvatinib plus pembrolizumab plus chemotherapy is superior to chemotherapy for ORR per RECIST 1.1 as assessed by BICR in participants with programmed cell death ligand 1 positive tumors defined by combined positive score ≥1. - Hypothesis (H6): Lenvatinib plus pembrolizumab plus chemotherapy is superior to chemotherapy for ORR per RECIST 1.1 as assessed by BICR in all participants.	- Objective Response: Complete response or partial response
- Objective (Part 2): To estimate DOR, per RECIST 1.1 as assessed by BICR for each treatment group in participants with programmed cell death ligand 1 combined positive score ≥1 and in all participants.	- Duration of Response: The time from first response (complete response or partial response) to subsequent disease progression, or death from any cause, whichever occurs first
- Objective (Part 2): To evaluate the safety and tolerability of lenvatinib plus pembrolizumab plus chemotherapy versus chemotherapy	- Adverse events - Study intervention discontinuation due to adverse events

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Gastrooesophageal cancer
Population	Male and female participants with first-line gastroesophageal adenocarcinoma
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 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:

The planned sample size for Part 1 (Safety Run-in) is approximately 12 participants. The planned sample size for Part 2 (Main Study) is approximately 878 participants who will be randomized as described in Section 9.9.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1	Pembrolizumab	25 mg/mL	400 mg	IV Infusion	Q6W	Test Product
Arm 1	Lenvatinib	10 mg/ 4 mg / 1mg	8 mg induction/ 20 mg consolidation	Oral	Once daily	Test Product
Arm 1	Capecitabine (CAPOX)	150 mg tablet or 500 mg tablet	1000 mg/m^2	Oral	BID for 14 days Q3W for 4 cycles	Test Product
Arm 1	Oxaliplatin (CAPOX)	100 mg/ 20 mL vial or 50 mg vial	130 mg/m^2	IV Infusion	Once Q3W for 4 cycles	Test Product
Arm 1	Oxaliplatin (mFOLFOX)	100 mg/ 20 mL vial or 50 mg vial	85 mg/m^2	IV Infusion	Once Q2W for 6 cycles	Test Product
Arm 1	5-FU (mFOLFOX)	500 mg/ 10 mL vial or 250 mg/ 10 mL vial	400 mg/m^2 (bolus) plus 2400 mg/m^2 (continuous)	IV Infusion	Q2W for 6 cycles	Test Product
Arm 1	Leucovorin or Levoleucovorin (mFOLFOX)	100 mg vial or 300 mg vial	400 mg/m² (or 200 mg/m² for levoleucovorin)	IV Infusion	Q2W for 6 cycles	Test Product
Arm 2	Capecitabine (CAPOX)	150 mg tablet or 500 mg tablet	1000 mg/m^2	Oral	bid for 14 days q3w	Comparator
Arm 2	Oxaliplatin (CAPOX)	100 mg/ 20 mL vial or 50 mg vial	130 mg/m^2	IV Infusion	q3w	Comparator
Arm 2	Oxaliplatin (mFOLFOX)	100 mg/ 20 mL vial or 50 mg vial	85 mg/m^2	IV Infusion	q2w	Comparator
Arm 2	5-FU (mFOLFOX)	500 mg/ 10 mL vial or 250 mg/ 10 mL vial	400 mg/m^2 (bolus) plus 2400 mg/m^2 (continuous)	IV Infusion	q2w	Comparator
Arm 2	Leucovorin or Levoleucovorin (mFOLFOX)	100 mg vial or 300 mg vial	400 mg/m² (or 200 mg/m² for levoleucovorin)	IV Infusion	q2w	Comparator

AxMP=auxiliary medical product; IMP=investigational medicinal product; IV=intravenous.; NIMP=noninvestigational medical product

The classification of IMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Investigator decision regarding the type of backbone chemotherapy (CAPOX or mFOLFOX6) should be determined prior to allocation/randomization. Participants should continue on the type of backbone chemotherapy chosen prior to randomization throughout the study.

Lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension (please refer to Pharmacy Manual).

Clinical supply concentration and formulation of chemotherapy may vary by local source.

Total Number of Intervention Groups/Arms	2 intervention groups
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final contact. After a Screening Phase of up to 28 days, each participant will be assigned to receive study treatment until one of the conditions for discontinuation of study intervention is met. Participants may continue treatment with lenvatinib beyond 2 years if they experience clinical benefit according to the PI, with Sponsor consultation and approval. Participants treated with pembrolizumab who complete 18 cycles (2 years) of treatment with stable disease or better or participants who attain an investigator-determined complete response and have received at least 4 cycles of pembrolizumab may be eligible for retreatment with up to an additional 9 cycles (approximately 1 year) of pembrolizumab if they experience radiographic disease progression verified by blinded independent central review after stopping treatment in the initial treatment phase. This retreatment is termed Second Course Treatment. Participants may continue treatment with pembrolizumab with or without lenvatinib during Second Course Treatment at the discretion of the investigator until meeting one of the criteria for treatment discontinuation. Note: As of Amendment 8, Second Course will no longer be offered. Any participant currently receiving Second Course retreatment will be able to continue treatment as planned. Imaging will be performed per local standard of care. Participants may be permitted to continue study intervention beyond Response Evaluation Criteria in Solid Tumors 1.1 defined disease progression as long as the treating investigator considers that the participant may experience clinical benefit with continued treatment, and the participant is tolerating study intervention. Request to validate progression by BICR must be submitted on disease progression assessed by investigator. Imaging should continue to be performed and submitted to the iCRO until any of the conditions for discontinuation of imaging are met. All decisions to continue treatment beyond BICR verified disease progression must be approved by the Sponsor.

	After study intervention completion/discontinuation, each participant will be followed for safety as described in Section 8.4. In addition, all participants will be followed for overall survival until death, withdrawal of consent, the end of the study, or enrollment into an extension study (if applicable). Participants who complete or discontinue study intervention in the absence of radiographic disease progression will have posttreatment follow-up imaging for disease status every 6 weeks until any of the conditions for discontinuation of imaging are met. Participants in Part 1 are expected to be treated with the full course of study treatment as depicted in Figure 1. The duration of the study for participants in Part 1 (Safety Run-in) and Part 2 (Main Study) is anticipated to be the same provided that the study passes Part 1 and moves to Part 2 (as detailed in Section 4.1, Figure 1 and Figure 2).

Study Governance Committees:

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

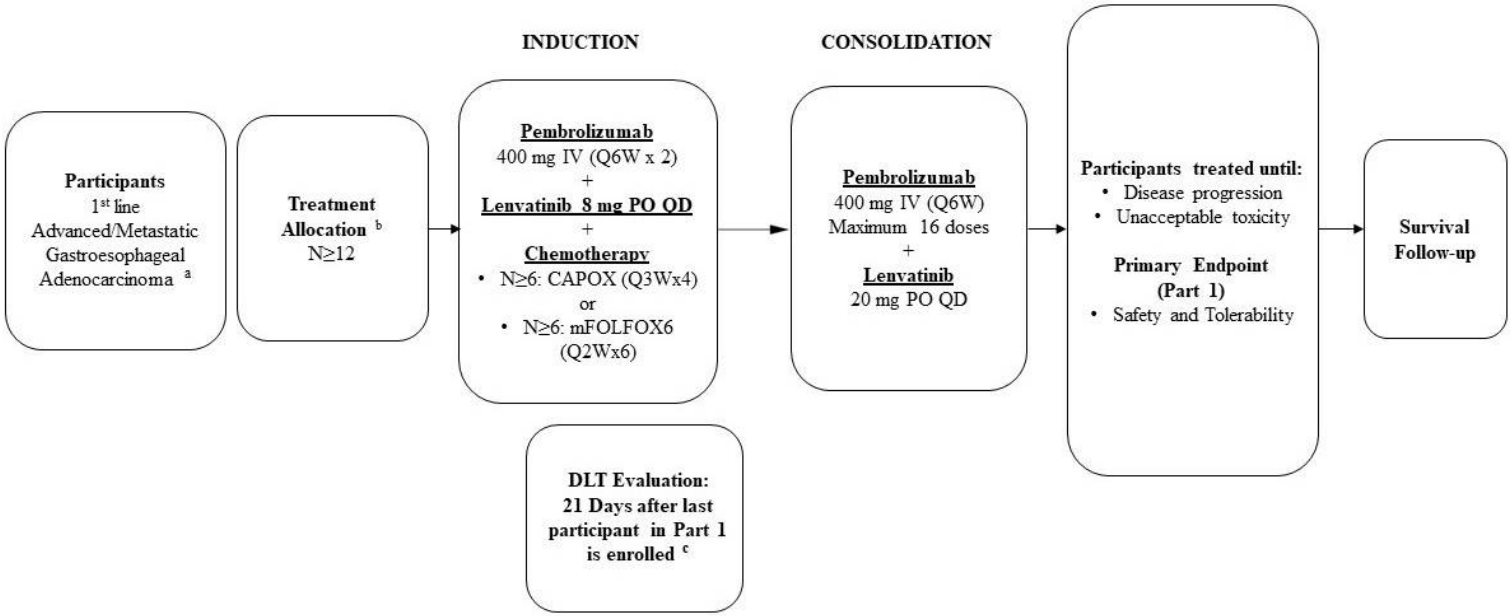
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1 (Part 1: Safety Run-in), Figure 2 (Part 2: Main Study) and Figure 3 (Second Course Treatment Phase). Note: As of Amendment 8, Second Course (Figure 3)will no longer be offered. Any participant currently receiving Second Course retreatment will be able to continue treatment as planned. Imaging will be performed per local standard of care.

Figure 1 Study Schema (Part 1: Safety Run-in)

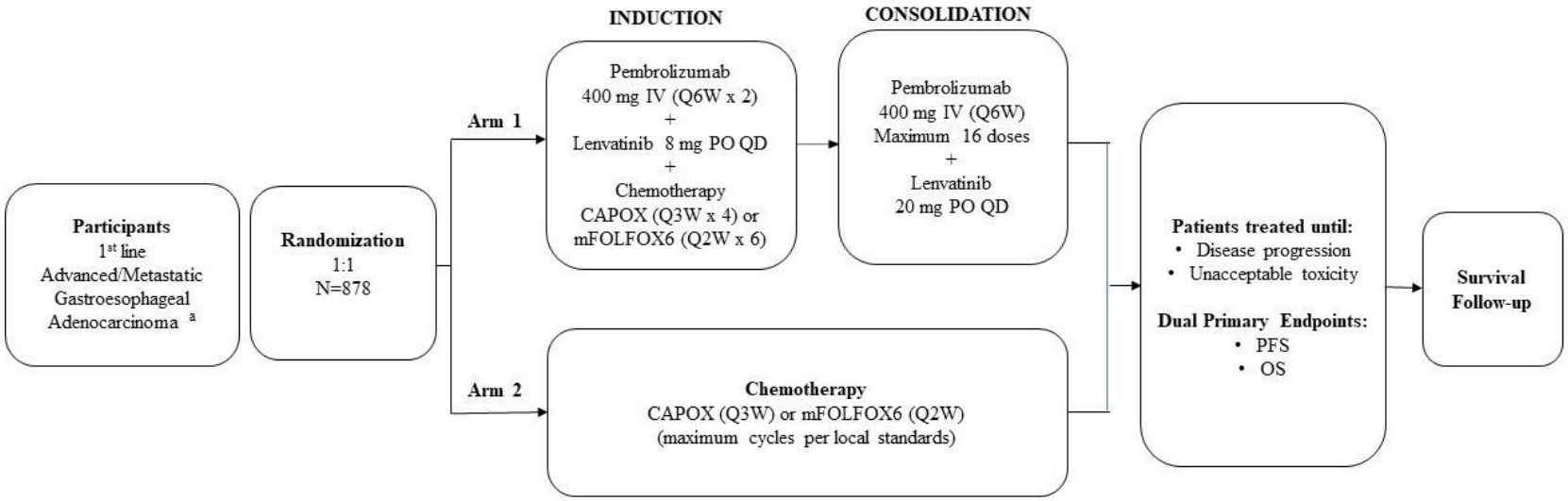


CAPOX=capecitabine + oxaliplatin; ECOG=Eastern Cooperative Oncology Group; mFOLFOX6=folinic acid, fluorouracil, and oxaliplatin; HER-2=human epidermal growth factor receptor 2; po=per oral; qd=once daily; QW6=dosing every 6 weeks.

a. HER-2 positive participants are excluded.
b. Selection of chemotherapy backbone by the investigator must be determined prior to allocation.
c. If 3 or more DLTs occur in either chemotherapy backbone treatment group during this Safety Run-in, enrollment to Part 2 may be delayed to further examine safety data and consider study design changes.

Note: After the last cycle of the Induction Phase, lenvatinib will be maintained at the current dose until the start of the Consolidation Phase. The Consolidation Phase, will begin 3 weeks after the last dose of oxaliplatin induction for CAPOX and 3 weeks after C2D29 of mFOLFOX6, when the dose will be escalated to 20 mg in participants who tolerated 8 mg. Participants who have had lenvatinib-related dose reductions during induction for hematologic toxicity may have dose escalation per Figure 2

Figure 2 Study Schema (Part 2: Main Study)



Stratification Factors:
- Region (East Asia, North America + Western Europe, Rest of World)
- ECOG (0 or 1)
- Intended Chemotherapy (CAPOX or mFOLFOX6)

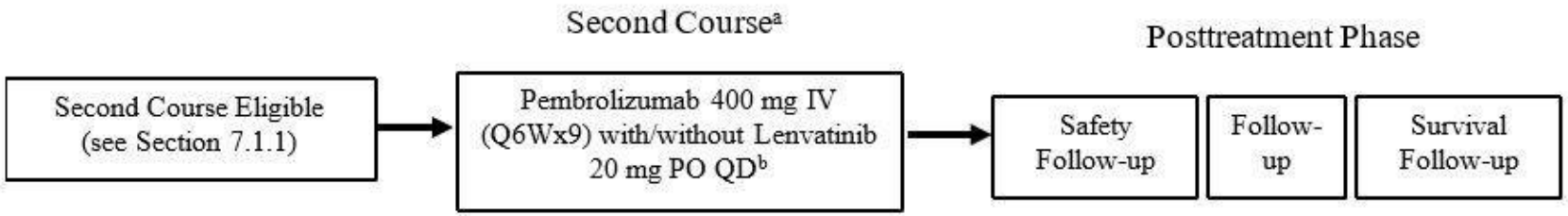
Dual Primary Endpoints: PFS and OS
Secondary Endpoint: ORR, DOR and Safety

CAPOX=capecitabine + oxaliplatin; DOR = duration of response; ECOG=Eastern Cooperative Oncology Group; mFOLFOX6=folinic acid, fluorouracil, and oxaliplatin; HER-2=human epidermal growth factor receptor 2; ORR = objective response rate; OS=overall survival; PFS=progression-free survival; po=per oral; qd=once daily; QW6=dosing every 6 weeks.

a. HER-2 positive participants are excluded.

Note: After the last cycle of the Induction Phase, lenvatinib will be maintained at the current dose until the start of the Consolidation Phase. The Consolidation Phase, will begin 3 weeks after the last dose of oxaliplatin induction for CAPOX and 3 weeks after C2D29 of mFOLFOX6, when the dose will be escalated to 20 mg in participants who tolerated 8 mg. Participants who have had lenvatinib-related dose reductions during induction for hematologic toxicity will have dose escalation per Table 7.

Figure 3 Second Course Treatment Phase



IV=intravenous; po=orally; Q6W=dosing every 6 weeks; qd=once daily.

Second Course is for eligible participants in both Part 1 and Part 2.

a. Second Course is up to 9 cycles of pembrolizumab (approximately 1 year), or meeting discontinuation criteria are listed in Section 7.1. Lenvatinib may continue beyond a year, per investigator's discretion.

b. Lenvatinib administration in the Second Course is at the discretion of the investigator. Lenvatinib may be restarted if the participant did not discontinue lenvatinib in the First Course due to lenvatinib-related AEs (Section 7.1). Lenvatinib will continue until meeting at least 1 of the discontinuation criteria listed in Section 7.1. Participants may begin the Second Course with lenvatinib at the highest tolerable dose received during the Consolidation Phase, per investigator's decision.

1.3 Schedule of Activities

1.3.1 Initial Treatment Phase: Lenvatinib Plus Pembrolizumab Plus CAPOX (Safety Run-in [Part 1] and Main Study [Part 2])

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	Screening	C1						C2	C3						C4 to 18	C>18	DC	Safety FU	FU Visits	Survival FU	
Cycle Day	-28 to -1	1	8	15	22	29	36	1 to 36	1	8	15	22	29	36	1 to 36	1 to 36					
Study Week		1	2	3	4	5	6	7 to 12	13	14	15	16	17	18			DC	30 Days Post Last Dose	Every 6 Weeks Post DC	Every 12 Weeks	
Scheduled Window (days):		3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
Administrative Procedures																					
Informed Consent	X																				Section 8.1.1.1
Reconsent at the first indication of radiographic recurrence/progression																					Assessed by the investigator before the next cycle starts.
Inclusion/Exclusion Criteria	X																				
Participant Identification Card	X	X																			Update at C1D1
Medical History	X																				
Prior/Concomitant Medication Review	X	X			X			X	X			X			X	X	X	X			Will be assessed on Day 1 and Day 22 of C2-C18. See Section 6.5
Treatment Randomization/allocation[c]		X																			
Survival Status	<----------																			X	Updated survival status may be requested by the Sponsor at any time during the course of the study.

Study Period[a]			**Screening**[b]	**Induction Phase (Cycles)**							**Consolidation Phase (Cycles)**								**EOT**	**Posttreatment**			**Notes**
Treatment Cycles			**Screening**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day			**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week				**1**	**2**	**3**	**4**	**5**	**6**	**7 to 12**	**13**	**14**	**15**	**16**	**17**	**18**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):				**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Study Treatment Administration																							
Pembrolizumab Administration				X						X	X						X						18 cycles, Q6W
Lenvatinib	Lenvatinib Dispense			X			X			X	X			X			X	X					Will be dispensed at Day 1 and Day 22 of all cycles after C2.
	Lenvatinib Administration			<---------->							<---------->												See Sections 6.6.3.1, 6.6.3.2, and 8.1.8.1 regarding dosing during Induction and Consolidation.
CAPOX administration	Oxaliplatin			X			X			X													130 mg/m^2 over ~2 hours At C2 will be administered at Day 1 and Day 22.
	Capecitabine	Capecitabine Dispense		X			X			X													At C2 will be dispensed at Day 1 and Day 22.
		Capecitabine Administration		<------>			<----->			X													1000 mg/m^2 BID on C1 and C2 Day 1 to 14 and Day 22 to 35
Clinical procedure and events																							
Adverse Events Monitoring				X	X[d]	X	X	X[d]	X	X	X	X[d]	X	X			X	X	X	X	X		Will be recorded on Day 1 and Day 22 of C2, and C4-C18, and at every clinic visit. AE reporting will be continuous throughout the study as detailed in Section 8.4.

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 12**	**13**	**14**	**15**	**16**	**17**	**18**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Full physical examination	X								X								X				At Screening, perform within 7 days prior to C1D1. If full physical examination is performed within 3 days before C1D1, directed physical examination for C1D1 could be skipped.
Directed physical examination		X		X	X		X	X			X	X			X	X					Will be performed on Day 1 and Day 22 of C2 and C4-C18.
Height	X																				
Weight and Vital Signs (including blood pressure)	X	X	X[d]	X	X	X[d]	X	X	X	X[d]	X	X			X	X	X				Will be performed on Day 1 and Day 22 of C2 and C4-C18
Telephone or virtual contact			X			X				X											Participant check of blood pressure and review of AEs
12-lead ECG with QTc measurement [e]	X	X			X			X	X			X			X	X	X	X			For country-specific requirements see Appendix 7.

Study Period[a]	**Screening**[b]	**Induction Phase (Cycles)**							**Consolidation Phase (Cycles)**								**EOT**	**Posttreatment**			**Notes**
Treatment Cycles	**Screening**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 12**	**13**	**14**	**15**	**16**	**17**	**18**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
ECHO/MUGA	X																X				A 14-day window for the assessment is allowed at EOT. Additional assessments may be performed as clinically indicated.
ECOG Performance Status	X				X			X	X			X			X	X	X	X			Will be assessed at Day 1 and Day 22 at C2-C18. ECOG status must be performed within 3 days of the beginning of Cycle 1 and prior to each systemic treatment administration.
Poststudy Anticancer Therapy Status																	X	X	X	X	

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	Screening	C1						C2	C3						C4 to 18	C>18	DC	Safety FU	FU Visits	Survival FU	
Cycle Day	-28 to -1	1	8	15	22	29	36	1 to 36	1	8	15	22	29	36	1 to 36	1 to 36					
Study Week		1	2	3	4	5	6	7 to 12	13	14	15	16	17	18			DC	30 Days Post Last Dose	Every 6 Weeks Post DC	Every 12 Weeks	
Scheduled Window (days):		3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
Patient-reported Outcomes																					
CCI [redacted]																					

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 12**	**13**	**14**	**15**	**16**	**17**	**18**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Tumor Tissue Collection																					
Tumor Blocks or Slides	X																				To include PD-L1 and MSI analysis. Central PD-L1 result will be masked to the site. A repeat sample will be required if submitted sample is inadequate. The planned MSI sample should be obtained at screening but may be collected post-randomization if needed.
Laboratory Assessments																					
Pregnancy Test – Urine or Serum	X	X			X			X	X			X			X	X	X	X[h]			Will be performed on Day 1 and Day 22 of C2 -C18. See Section 8.3.6. WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention and before each subsequent testing day as indicated.
FSH (in WONCBP only)	X																				

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 12**	**13**	**14**	**15**	**16**	**17**	**18**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
PT/INR and aPTT[f]	X																				After baseline, PT/INR should be tested as needed for participants on warfarin-based anticoagulation therapy.
CBC with Differential[f]	X				X			X	X			X			X	X	X	X			Will be assessed on Day 1 and Day 22 of C2-C18. Starting from C19 it will be assessed on Day 1 of every cycle.
Chemistry Panel[f]	X			X	X		X	X	X		X	X			X	X	X	X			Will be assessed on Day 1 and Day 22 of C2 and every cycle from C4 onwards.
C-reactive protein[f]	X								X												Screening and Cycle 3 only
Urine Dipstick (Urinalysis)[f, g]	X			X	X		X	X	X		X	X			X	X	X				At C2 will be assessed at Day 1 and Day 22. After Cycle 3, urine dipstick testing for protein will be performed within 3 days before Day 1 and Day 22 of every cycle while participants are taking lenvatinib.

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 12**	**13**	**14**	**15**	**16**	**17**	**18**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
HIV, Hepatitis B and C screen	X																				Required at baseline. only if mandated by local health authority or as clinically indicated (see Appendix 7).
Thyroid function (T3, T4, and TSH)	X							X	X						X	X	X	X			Should be performed at Day 1 of every Cycle. Free T3 and Free T4 are acceptable. Participants may be dosed while thyroid function tests are pending.
Plasma Sample for Lenvatinib PK		X			X				X												C1D1: 0.5 to 4 and 6 to 10 hours post dose C1D22: predose, and 2 to 12 hours postdose C3D1: predose, 0.5 to 4 and 6 to 10 hours postdose. All predose samples should be collected within 2 hours of lenvatinib administration. Postdose samples are not needed if lenvatinib administration is skipped.

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 12**	**13**	**14**	**15**	**16**	**17**	**18**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Serum for Pembrolizumab PK		X							X												Prior to pembrolizumab infusion on C1D1 and C3D1.
Antipembrolizumab Antibodies		X							X												Prior to pembrolizumab infusion on C1D1 and C3D1.
CCI																					

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	Screening	C1						C2	C3						C4 to 18	C>18	DC	Safety FU	FU Visits	Survival FU	
Cycle Day	-28 to -1	1	8	15	22	29	36	1 to 36	1	8	15	22	29	36	1 to 36	1 to 36					
Study Week		1	2	3	4	5	6	7 to 12	13	14	15	16	17	18			DC	30 Days Post Last Dose	Every 6 Weeks Post DC	Every 12 Weeks	
Scheduled Window (days):		3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
CCI																					

Study Period[a]	Screening[b]	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 12**	**13**	**14**	**15**	**16**	**17**	**18**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Efficacy Assessment																					
Tumor Imaging (CT/MRI)	X	See note for tumor imaging schedule																			The initial imaging must be performed within 28 days of randomization. The first on-study imaging assessment should be performed 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. If imaging was obtained within 4 weeks prior to EOT, a scan at EOT is not mandatory. As of Amendment 8, on-study imaging is no longer required and should be performed per local standard of care.

aPTT/PTT=activated partial thromboplastin time/partial thromboplastin time; BID=twice daily; CBC=complete blood count; CAPOX=capecitabine + oxaliplatin; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DC=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiograph, ECHO/MUGA=echocardiogram/multiple gated acquisition scan; ECOG=Eastern Cooperative Oncology Group; EDTA=ethylenediamine tetraacetic acid; EQ-5D 5L=EuroQoL 5 Dimension Questionnaire; EORTC QLQ C30=European Organization for Research & Treatment of Cancer Quality-of-Life Questionnaire global health status; EORTC QLQ-ST022=European Organization for Research & Treatment of Cancer Quality-of-Life Questionnaire (Symptom Score for ST022); EOT=end of treatment; FSH=follicle-stimulating hormone; FT3=free T3 thyroid hormone; FT4=free thyroxine; FU=Follow-up; HBV= hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; MSI=microsatellite instability; PD-L1=programmed death-ligand 1; PET=positron emission tomography; PK=pharmacokinetic; ePRO=electronic patient-reported outcomes; PT=prothrombin time; QW3=dosing every 3 weeks; QW6=dosing every 6 weeks; RECIST=Response Evaluation Criteria in Solid Tumors 1.1; RNA=ribonucleic acid; SAE=serious adverse event; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential; WONCBP=woman of nonchild-bearing potential.

a. No stratification in Part 1 (Safety-Run-in).
b. Screening procedures may be performed on the day of randomization; participant eligibility must be confirmed before randomization.
c. Dose within 3 days of randomization.
d. A phone or virtual visit by investigator or designee will be scheduled to report blood pressure and record adverse events. Full vital signs assessment is not required. Blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee.
e. 6-lead ECG is allowed per institutional standard. Induction Phase (CAPOX): ECG at Screening, C1D1, C1D22. C2D1, and C2D22. ECGs in the Induction Phase should be performed approximately 2 hours post lenvatinib dose. Consolidation Phase (CAPOX): C3D1 and C3D22, and starting from C5, an ECG should be performed every 2 cycles (12 weeks). For high-risk participants (as defined in Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, an ECG is only required at EOT and Safety Follow-up Visits.
f. Screening laboratory assessments (PT/INR and aPTT, CBC, chemistry, C-reactive protein and urine dipstick) MUST be performed within 10 days of C1D1 or on C1D1 as long as results are available prior to administration of study intervention. Results from the most recent laboratory tests must be used to assess participant eligibility. After C1, predose laboratory procedures can be conducted up to 72 hours prior to dosing.
g. Dipstick is preferred but urinalysis may be used if the use of urine dipstick is not feasible. If a urine dipstick is abnormal follow Section 6.6.3.5. If lenvatinib is discontinued, urine dipstick is only required at EOT visit.
h. Pregnancy testing is required at the Safety Follow-up visit and at the end of relevant systemic exposure

1.3.2 Initial Treatment Phase: Lenvatinib Plus Pembrolizumab Plus mFOLFOX6 (Safety Run-in [Part 1] and Main Study [Part 2])

Study Period[a]		Screening	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles		**Screening[b]**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day		**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week			**1**	**2**	**3**	**4**	**5**	**6**	**7 to 13**	**14**	**15**	**16**	**17**	**18**	**19**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):			**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Administrative Procedures																						
Informed Consent		X																				Section 8.1.1.1
Reconsent at the first indication of radiographic recurrence/progression																						Assessed by the investigator before the next cycle starts
Inclusion/Exclusion Criteria		X																				
Participant Identification Card		X	X																			Update at C1D1
Medical History		X																				
Prior/Concomitant Medication Review		X	X		X		X		X	X			X			X	X	X	X			At C2 will be assessed on Day 1, Day 15, and Day 29. Will be assessed on Day 1 and Day 22 of C4-C18. See Section 6.5
Treatment Randomization[c]			X																			
Survival Status		<---------->																			X	Updated survival status may be requested by the Sponsor at any time during the course of the study.
Study Treatment Administration																						
Pembrolizumab Administration			X						X	X						X						18 cycles, Q6W
Lenvatinib	Lenvatinib Dispense		X		X		X		X	X			X			X	X					At C2 will be dispensed on Day 1, Day 15, and Day 29. Will be dispensed on Day 1 and Day 22 of C3-C18.
	Lenvatinib Administration	<---------->								<---------->							X					See Sections 6.6.3.1, 6.6.3.2, and 8.1.8.1 regarding dosing during Induction and Consolidation.

Study Period[a]		**Screening**	**Induction Phase (Cycles)**							**Consolidation Phase (Cycles)**								**EOT**	**Posttreatment**			**Notes**
Treatment Cycles		**Screening**[b]	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day		**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week			**1**	**2**	**3**	**4**	**5**	**6**	**7 to 13**	**14**	**15**	**16**	**17**	**18**	**19**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):			**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
mFOLFOX6 administration	Oxaliplatin		X		X		X		X													Oxaliplatin administration 85 mg/m^2 over ~2 hours. Consolidation C3D1 should start 3 weeks after C2D29 (ie, 3 weeks after last dose of oxaliplatin)
	Leucovorin/ levoleucovorin		X		X		X		X													
	5-FU Bolus		X		X		X		X													400 mg/m^2 IV
	5-FU		X		X		X		X													2400 mg/m^2 continuous IV
Clinical procedure and events																						
Adverse Events Monitoring			X	X[d]	X		X		X	X	X[d]	X	X			X	X	X	X	X		At C2 will be recorded on Day 1, Day 15, and Day 29. Will also be recorded on Day 1 and Day 22 of C4-C18. AE reporting will be continuous throughout the study as detailed in Section 8.4.
Full physical examination		X								X								X				At Screening, perform within 7 days prior to C1D1. If full physical examination is performed within 3 days before C1D1, directed physical examination for C1D1 could be skipped.
Directed physical examination			X		X		X		X			X	X			X	X					At C2 will be assessed at Day 1, Day 15, and Day 29. Will also be assessed on Day 1 and Day 22 of C4-C18.
Height		X																				

Study Period[a]	Screening	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening[b]**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 13**	**14**	**15**	**16**	**17**	**18**	**19**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Weight and Vital Signs (including blood pressure)	X	X	X[d]	X		X		X	X	X[d]	X	X			X	X	X				At C2 will be assessed on Day1, Day 15, and Day 29. Will also be assessed on Day 1 and Day 22 of C4-C18.
Telephone or virtual contact			X							X											Participant check of blood pressure and review of AEs
12-lead ECG with QTc measurement [e]	X	X		X				X	X			X			X	X	X	X			See Appendix 7 for country-specific requirements.
ECHO/MUGA	X																X				A 14-day window for the assessment is allowed at EOT. Additional assessments may be performed as clinically indicated.
ECOG Performance Status	X			X		X		X	X			X			X	X	X	X			At C2 will be performed on Day 1, Day 15, and Day 29. Will be performed on Day 1 and Day 22 of C4-C18. ECOG Status must be performed within **3 days** of beginning of Cycle 1 and prior to each systemic treatment administration.
Poststudy Anticancer Therapy Status																	X	X	X	X	

Study Period[a]	Screening	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	Screening[b]	C1						C2	C3						C4 to 18	C>18	DC	Safety FU	FU Visits	Survival FU	
Cycle Day	-28 to -1	1	8	15	22	29	36	1 to 36	1	8	15	22	29	36	1 to 36	1 to 36					
Study Week		1	2	3	4	5	6	7 to 13	14	15	16	17	18	19			DC	30 Days Post Last Dose	Every 6 Weeks Post DC	Every 12 Weeks	
Scheduled Window (days):		3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
Patient-reported Outcomes																					
CCI [redacted]																					
Tumor Tissue Collection																					
Tumor Blocks or Slide	X																				To include PD-L1 and MSI analysis. Central PD-L1 result will be masked to the site. A repeat sample will be required if submitted sample is inadequate. The planned MSI sample should be obtained at screening but may be collected post-randomization if needed.

Study Period[a]	Screening	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening[b]**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 13**	**14**	**15**	**16**	**17**	**18**	**19**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Laboratory Assessments																					
Pregnancy Test – Urine or Serum	X	X		**X**		X		X	X			X			X	X	X	X[h]			At C2 will be assessed on Day 1, Day 15, and Day 29. Will also be assessed on Day 1 and Day 22 of C4-C18. WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention and before each subsequent testing day as indicated. See Section 8.3.6.
FSH (WONCBP only)	X																				
PT/INR and aPTT[f]	X																				After baseline, PT/INR should be tested as needed for participants on warfarin-based anticoagulation therapy.
CBC with Differential[f]	X			X		X		X	X			X			X	X	X	X			At C2 will be assessed on Day 1, Day 15, and Day 29. Will also be assessed on Day 1 and Day 22 of C4-C18. Starting from C19 it will be assessed on Day 1 of every cycle.
Chemistry Panel[f]	X			X		X		X	X		X	X			X	X	X	X			At C2 will be assessed at Day 1, Day 15, and Day 29. Will be assessed on Day 1 and Day 22 of every cycle from C4 onwards.
C-reactive protein[f]	X								X												Screening and Cycle 3 only

Study Period[a]	Screening	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	Screening[b]	C1						C2	C3						C4 to 18	C>18	DC	Safety FU	FU Visits	Survival FU	
Cycle Day	-28 to -1	1	8	15	22	29	36	1 to 36	1	8	15	22	29	36	1 to 36	1 to 36					
Study Week		1	2	3	4	5	6	7 to 13	14	15	16	17	18	19			DC	30 Days Post Last Dose	Every 6 Weeks Post DC	Every 12 Weeks	
Scheduled Window (days):		3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
Urine Dipstick (Urinalysis)[f, g]	X			X		X		X	X		X	X			X	X	X				At C2 will be assessed at Day 1, Day 15, and Day 29. After Cycle 3, urine dipstick testing for protein will be performed within 3 days before Day 1 and Day 22 of every cycle while participants are taking lenvatinib.
HIV, Hepatitis B and C screen	X																				Required at baseline only if mandated by local health authority or as clinically indicated (Appendix 7).
Thyroid function (T3, T4, and TSH)	X							X	X						X	X	X	X			Should be performed on Day 1 of every Cycle. Free T3 and Free T4 are acceptable. Participants may be dosed while thyroid function tests are pending.
Plasma Sample for Lenvatinib PK		X		X					X												C1D1: 0.5 to 4 and 6 to 10 hours postdose C1D15: predose, and 2 to 12 hours postdose C3D1: predose, 0.5 to 4 and 6 to 10 hours postdose. All predose samples should be collected within 2 hours of lenvatinib administration. Postdose samples are not needed if lenvatinib administration is skipped.

Study Period[a]	Screening	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening[b]**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 13**	**14**	**15**	**16**	**17**	**18**	**19**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Serum for Pembrolizumab PK		X							X												Prior to pembrolizumab infusion on C1D1 and C3D1.
Antipembrolizumab Antibodies		X							X												Prior to pembrolizumab infusion on C1D1 and C3D1.
CCI [redacted]																					

Study Period[a]	Screening	Induction Phase (Cycles)							Consolidation Phase (Cycles)								EOT	Posttreatment			Notes
Treatment Cycles	**Screening[b]**	**C1**						**C2**	**C3**						**C4 to 18**	**C>18**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 13**	**14**	**15**	**16**	**17**	**18**	**19**			**DC**	**30 Days Post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 Weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
Efficacy Assessment																					
Tumor Imaging (CT/MRI)	X	See note for tumor imaging schedule																			Tumor Imaging (CT/MRI) The initial imaging must be performed within 28 days of randomization. The first on-study imaging assessment should be performed 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. If imaging was obtained within 4 weeks prior to EOT, a scan at EOT is not mandatory. As of Amendment 8, on-study imaging is no longer required and should be performed per local standard of care.

5-FU=5-fluoruracil; aPTT/PTT=activated partial thromboplastin time/partial thromboplastin time; BID=twice daily; CBC=complete blood count; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DC=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiograph, ECHO/MUGA=echocardiogram/multiple gated acquisition scan; ECOG=Eastern Cooperative Oncology Group; EDTA= ethylenediamine tetraacetic acid; EQ-5D 5L=EuroQoL 5 Dimension Questionnaire; EORTC QLQ C30=European Organization for Research & Treatment of Cancer Quality-of-Life Questionnaire global health status; EORTC QLQ-ST022=European Organization for Research & Treatment of Cancer Quality-of-Life Questionnaire (Symptom Score for ST022); EOT=end of treatment; mFOLFOX6=folinic acid, fluorouracil, and oxaliplatin; FSH=follicle-stimulating hormone; FT3=free T3 thyroid hormone; FT4=free thyroxine; FU=Follow-up; HBV= hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; MSI= microsatellite instability; PD-L1=programmed death-ligand 1; PET=positron emission tomography; PK=pharmacokinetic; ePRO= electronic patient-reported outcomes; PT=prothrombin time; QW3=dosing every 3 weeks; QW6=dosing every 6 weeks; RECIST=Response Evaluation Criteria in Solid Tumors 1.1; RNA=ribonucleic acid; SAE=serious adverse event; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential; WONCBP=woman of nonchild-bearing potential.

a. No stratification in Part 1 (Safety-Run-in).
b. Screening procedures may be performed on the day of randomization; participant eligibility must be confirmed before randomization.
c. Dose within 3 days of randomization.
d. A phone or virtual visit will be scheduled to report blood pressure and record adverse events. Full vital signs assessment is not required blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee.
e. 6-lead ECG is allowed per institutional standard. Induction Phase (mFOLFOX6): ECG at Screening, C1D1, C1D15, C2D1, and C2D15. ECGs in induction should be performed approximately 2 hours post lenvatinib dose. Consolidation Phase (mFOLFOX6): C3D1 and C3D22; and starting from C5, ECG should be performed every second cycle (12 weeks). For high-risk participants (as defined in Section 8.3.3), conduct ECG monitoring every Cycle. If lenvatinib is discontinued, an ECG is only required at EOT and Safety Follow-up Visits.
f. Screening laboratory assessments (PT/INR and aPTT, CBC, C-reactive protein, chemistry and urine dipstick) MUST be performed within 10 days of C1D1 or on C1D1 as long as results are available prior to administration of study intervention. Results from the most recent laboratory tests must be used to assess participant eligibility. After C1, predose laboratory procedures can be conducted up to 72 hours prior to dosing.
g. Dipstick is preferred but urinalysis may be used if the use of urine dipstick is not feasible. If lenvatinib is discontinued, urine dipstick is only required at EOT visits.
h. Pregnancy testing is required at the Safety Follow-up visit and at the end of relevant systemic exposure.

1.3.3 CAPOX Only (Main Study [Part 2])

Study Period			Screening	Treatment Phase							EOT	Posttreatment			Notes
Treatment Cycles			Screening[a]	C1						C2 to 18[b]	DC	Safety FU	FU Visits	Survival FU	
Cycle Day			-28 to -1	1	8	15	22	29	36	1 to 36					
Study Week				1	2	3	4	5	6		DC	30 Days post Last Dose	Every 6 Weeks Post DC	Every 12 weeks	
Scheduled Window (days):				3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
Administrative Procedures															
Informed Consent			X												Section 8.1.1.1
Reconsent at the first indication of radiographic recurrence/progression															Assessed by the investigator
Inclusion/Exclusion Criteria			X												
Participant Identification Card			X	X											Update at C1D1
Medical History			X												
Prior/Concomitant Medication Review			X	X			X			X	X	X			At C2-C18 will be assessed at Day 1 and Day 22. See Section 6.5
Treatment Randomization[c]				X											
Survival Status			<----------											X	Updated survival status may be requested by the Sponsor at any time during the course of the study.
Study Treatment Administration															
CAPOX	Oxaliplatin			X			X			X					
	Capecitabine	Capecitabine Dispense		X			X			X					At C2-C18 will be dispensed at Day 1 and Day 22.
		Capecitabine Administration		<----------			<----------			X					1000 mg/m^2 BID on Day 1 to 14 and Day 22 to 35 of every cycle
Clinical Procedures/Assessments															
Adverse Events Monitoring				X			X			X	X	X	X		At C2-C18 will be recorded at Day 1 and Day 22. AE reporting will be continuous throughout the study as detailed in Section 8.4.
Full Physical Examination			X								X				At Screening, perform within 7 days prior to C1D1. If full physical examination is performed within 3 days before C1D1, directed physical examination for C1D1 could be skipped.
Directed Physical Examination				X			X			X					At C2-C18 will be assessed at Day 1 and Day 22.
Height			X												
Weight and Vital Signs			X	X			X			X	X				At C2-C18 will be assessed at Day 1 and Day 22.
12-lead ECG with QTc measurement[d]			X								X	X			For country-specific requirements see Appendix 7.
ECHO/MUGA			X												Additional assessments may be performed as clinically indicated.

Study Period	Screening	Treatment Phase							EOT	Posttreatment			Notes
Treatment Cycles	**Screening[a]**	**C1**						**C2 to 18[b]**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**		**DC**	**30 Days post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
ECOG Performance Status	X				X			X	X	X			Will be assessed on Day 1 and Day 22 of C2-C18. ECOG Status must be performed within **3 days** of beginning of Cycle 1 and prior to each systemic treatment administration.
Poststudy Anticancer Therapy Status									X	X	X	X	
Patient-reported Outcomes													
CCI [redacted]													
Tumor Tissue Collection													
Tumor Blocks or Slides	X												To include PD-L1 and MSI analysis Central PD-L1 result will be masked to the site. A repeat sample will be required if submitted sample is inadequate. The planned MSI sample should be obtained at screening but may be collected post-randomization if needed.
Laboratory Assessments													
Pregnancy Test – Urine or Serum	X	X			X			X	X	X[g]			Will be assessed on Day 1 and Day 22 of C2-C18. WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention and before each subsequent testing day as indicated. See Section 8.3.6.
FSH (WONCBP only)	X												
PT/INR and aPTT[e]	X												After baseline, PT/INR should be tested as needed for participants on warfarin-based anticoagulation therapy.
CBC with Differential[e]	X				X			X	X	X			Will be assessed on Day 1 and Day 22 of C2-C18.
Chemistry Panel[e]	X				X			X	X	X			Will be assessed on Day 1 and Day 22 of C2-C18.
C-reactive protein[e]	X							X					Screening and Cycle 3 only
Urine dipstick (Urinalysis)[e, f]	X								X				

Study Period	Screening	Treatment Phase							EOT	Posttreatment			Notes
Treatment Cycles	Screening[a]	C1						C2 to 18[b]	DC	Safety FU	FU Visits	Survival FU	
Cycle Day	-28 to -1	1	8	15	22	29	36	1 to 36					
Study Week		1	2	3	4	5	6		DC	30 Days post Last Dose	Every 6 Weeks Post DC	Every 12 weeks	
Scheduled Window (days):		3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
HIV, Hepatitis B and C screen	X												Required at baseline. only if mandated by local health authority or as clinically indicated (see Appendix 7).
Thyroid function (T3, T4, and TSH)	X							X	X	X			Should be performed at Day 1 of every Cycle. Free T3 and Free T4 are acceptable. Participants may be dosed while thyroid function tests are pending.
CCI [redacted]													
Efficacy Assessment													
Tumor Imaging (CT/MRI)	X	See note for tumor imaging schedule											Tumor Imaging (CT/MRI) The initial imaging must be performed within 28 days of randomization. The first on-study imaging assessment should be performed 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. If imaging was obtained within 4 weeks prior to EOT, a scan at EOT is not mandatory. As of Amendment 8, on-study imaging is no longer required and should be performed per local standard of care.

aPTT/PTT=activated partial thromboplastin time/partial thromboplastin time; BID=twice daily; CBC=complete blood count; CAPOX= capecitabine + oxaliplatin; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DC=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiograph; ECHO/MUGA=echocardiogram/multiple gated acquisition scan; ECOG=Eastern Cooperative Oncology Group; EDTA= ethylenediamine tetraacetic acid; EQ-5D 5L=EuroQoL 5 Dimension Questionnaire; EORTC QLQ C30=European Organization for Research & Treatment of Cancer Quality-of-Life Questionnaire global health status; EORTC QLQ-ST022=European Organization for Research & Treatment of Cancer Quality-of-Life Questionnaire (Symptom Score for ST022); EOT=end of treatment; FSH=follicle-stimulating hormone; FT3=free T3 thyroid hormone; FT4=free thyroxine; FU=Follow-up; HBV= hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; MSI= microsatellite instability; PD-L1=programmed death-ligand 1; PET=positron emission tomography; PK=pharmacokinetic; ePRO= electronic patient-reported outcomes; PT=prothrombin time; QW3=dosing every 3 weeks; QW6=dosing every 6 weeks; RECIST=Response Evaluation Criteria in Solid Tumors 1.1; RNA=ribonucleic acid; SAE=serious adverse event; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential; WONCBP=woman of nonchild-bearing potential.

a. Screening procedures may be performed on the day of randomization; participant eligibility must be confirmed before randomization.
b. C2-C18 should have the same visits as C1.
c. Dose within 3 days of randomization.
d. 6-lead ECG is allowed per institutional standard.
e. Screening laboratory assessments (PT/INR and aPTT, CBC, chemistry, C-reactive protein and urine dipstick) MUST be performed within 10 days of C1D1 or on C1D1 as long as results are available prior to administration of study intervention. Results from the most recent laboratory tests must be used to assess participant eligibility. After C1, pre dose laboratory procedures can be conducted up to 72 hours prior to dosing.
f. Dipstick is preferred but urinalysis may be used if the use of urine dipstick is not feasible.
g. Pregnancy testing is required at the Safety Follow-up visit and at the end of relevant systemic exposure

1.3.4 mFOLFOX6 Only (Main Study [Part 2])

Study Period		Screening	Treatment Phase							EOT	Posttreatment			Notes
Treatment Cycles		Screening[a]	C1						C2 to 18[b]	DC	Safety FU	FU Visits	Survival FU	
Cycle Day		-28 to -1	1	8	15	22	29	36	1 to 36					
Study Week			1	2	3	4	5	6		DC	30 Days post Last Dose	Every 6 Weeks Post DC	Every 12 weeks	
Scheduled Window (days):			3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
Administrative Procedures														
Informed Consent		X												Section 8.1.1
Reconsent at the first indication of radiographic recurrence/progression														As assessed by the investigator
Inclusion/Exclusion Criteria		X												
Participant Identification Card		X	X											Update at C1D1
Medical History		X												
Prior/Concomitant Medication Review		X	X		X		X		X	X	X			At C2-C18 will be assessed on Day 1, Day 15, and Day 29. See Section 6.5
Treatment Randomization[c]			X											
Survival Status		<----------											X	Updated survival status may be requested by the Sponsor at any time during the course of the study.
Study Treatment Administration														
mFOLFOX6 administration	Oxaliplatin		X		X		X		X					
	Leucovorin/levoleucovorin		X		X		X		X					
	5-FU Bolus		X		X		X		X					400 mg/m^2 IV
	5-FU		X		X		X		X					2400 mg/m^2 continuous IV
Clinical Procedures/Assessments														
Adverse Events Monitoring			X		X		X		X	X	X	X		At C2-C18 will be recorded on Day 1, Day 15, and Day 29. AE reporting will be continuous throughout the study as detailed in Section 8.4.
Full physical examination		X								X				At Screening, perform within 7 days prior to C1D1. If full physical examination is performed within 3 days before C1D1, directed physical examination for C1D1 could be skipped.
Directed physical examination			X		X		X		X					At C2-C18 will be assessed on Day 1, Day 15, and Day 29.
Height		X												
Weight and Vital Signs		X	X		X		X		X	X				At C2-C18 will be assessed on Day 1, Day 15, and Day 29.
12-lead ECG with QTc measurement[d]		X								X	X			For country-specific requirements see Appendix 7.
ECHO/MUGA		X												Additional assessments may be performed as clinically indicated.

Study Period	Screening	Treatment Phase							EOT	Posttreatment			Notes
Treatment Cycles	**Screening[a]**	**C1**						**C2 to 18[b]**	**DC**	**Safety FU**	**FU Visits**	**Survival FU**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1 to 36**					
Study Week		**1**	**2**	**3**	**4**	**5**	**6**		**DC**	**30 Days post Last Dose**	**Every 6 Weeks Post DC**	**Every 12 weeks**	
Scheduled Window (days):		**3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	
ECOG Performance Status	X			X		X		X	X	X			Will be assessed on Day 1, Day 15, and Day 29 of C2-C18. ECOG Status must be performed within **3 days** of beginning of Cycle 1 and prior to each systemic treatment administration.
Poststudy Anticancer Therapy Status									X	X	X	X	
Patient-reported Outcomes													
CCI [redacted]													
Tumor Tissue Collection													
Tumor Blocks or Slides	X												To include PD-L1 and MSI analysis. Central PD-L1 result will be masked to the site. A repeat sample will be required if submitted sample is inadequate. The planned MSI sample should be obtained at screening but may be collected post-randomization if needed.
Laboratory Assessments													
Pregnancy Test – Urine or Serum	X	X		X		X		X	X	X[g]			Will be assessed on Days 1, 15 and 29 of C2 to C18 WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention and before each subsequent testing day as indicated. See Section 8.3.6.
FSH (WONCBP only)	X												
PT/INR and aPTT[e]	X												After baseline, PT/INR should be tested as needed for participants on warfarin-based anticoagulation therapy.
CBC with Differential[e]	X			X		X		X	X	X			Will be assessed on Days 1, 15 and 29 of C2 to C18.
Chemistry Panel[e]	X			X		X		X	X	X			Will be assessed on Days 1, 15 and 29 of C2 to C18.
C-reactive protein[e]	X							X					Screening and Cycle 3 only
Urine dipstick (Urinalysis)[e, f]	X								X				
HIV, Hepatitis B and C screen	X												Required at baseline only if mandated by local health authority or as clinically indicated (Appendix 7).
Thyroid function (T3, T4, and TSH)	X							X	X	X			Should be performed at Day 1 of every Cycle. Free T3 and Free T4 are acceptable. Participants may be dosed while thyroid function tests are pending.

Study Period	Screening	Treatment Phase							EOT	Posttreatment			Notes
Treatment Cycles	Screening[a]	C1						C2 to 18[b]	DC	Safety FU	FU Visits	Survival FU	
Cycle Day	-28 to -1	1	8	15	22	29	36	1 to 36					
Study Week		1	2	3	4	5	6		DC	30 Days post Last Dose	Every 6 Weeks Post DC	Every 12 weeks	
Scheduled Window (days):		3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	
CCI													
Efficacy Assessment													
Tumor Imaging (CT/MRI)	X	See note for tumor imaging schedule											Tumor Imaging (CT/MRI) The initial imaging must be performed within 28 days of randomization. The first on-study imaging assessment should be performed 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. If imaging was obtained within 4 weeks prior to EOT, a scan at EOT is not mandatory. As of Amendment 8, on-study imaging is no longer required and should be performed per local standard of care.

aPTT/PTT=activated partial thromboplastin time/partial thromboplastin time; BID=twice daily; CBC=complete blood count; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DC=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiograph, ECHO/MUGA= echocardiogram/multiple gated acquisition scan; ECOG=Eastern Cooperative Oncology Group; EDTA= ethylenediamine tetraacetic acid; EQ-5D 5L=EuroQoL 5 Dimension Questionnaire; EORTC QLQ C30=European Organization for Research & Treatment of Cancer Quality-of-Life Questionnaire global health status; EORTC QLQ-ST022=European Organization for Research & Treatment of Cancer Quality-of-Life Questionnaire (Symptom Score for ST022); EOT=end of treatment; mFOLFOX6= folinic acid, fluorouracil, and oxaliplatin; FSH=follicle-stimulating hormone; FT3=free T3 thyroid hormone; FT4=free thyroxine; FU=Follow-up; HBV= hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; IRT=interactive response technology; MRI=magnetic resonance imaging; MSI= microsatellite instability; PD-L1=programmed death-ligand 1; PET=positron emission tomography; PK=pharmacokinetic; ePRO= electronic patient-reported outcomes; PT=prothrombin time; QW3=dosing every 3 weeks; QW6=dosing every 6 weeks; RECIST=Response Evaluation Criteria in Solid Tumors 1.1; RNA=ribonucleic acid; SAE=serious adverse event; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential; WONCBP=woman of nonchild-bearing potential.

a. Screening procedures may be performed on the day of randomization; participant eligibility must be confirmed before randomization.
b. C2-C18 should have the same visits as C1.
c. Dose within 3 days of randomization.
d. 6-lead ECG is allowed per institutional standard.
e. Screening laboratory assessments (PT/INR and aPTT, CBC, C-reactive protein, chemistry and urine dipstick) MUST be performed within 10 days of C1D1 or on C1D1 as long as results are available prior to administration of study intervention. Results from the most recent laboratory tests must be used to assess participant eligibility. After C1, predose laboratory procedures can be conducted up to 72 hours prior to dosing.
f. Dipstick is preferred but urinalysis may be used if the use of urine dipstick is not feasible.
g. Pregnancy testing is required at the Safety Follow-up visit and at the end of relevant systemic exposure.

1.3.5 Second Course (Part 1 and Part 2)

Note: As of Amendment 8, Second Course will no longer be offered. Any participant currently receiving Second Course treatment will be able to continue treatment as planned. Imaging will be performed per local standard of care. Participants who either complete 18 cycles of pembrolizumab or discontinue pembrolizumab will be discontinued from the study following the Safety Follow-up visit. AE, SAE, and other reportable safety events will be reported and followed as described under Section 8.4. All participants in Efficacy Follow-up prior to initiation of Amendment 8 will stop efficacy assessments and be discontinued from the study. All participants in Survival Follow-up are considered to have completed the study and should have a final survival contact; these participants will no longer be contacted for survival information. The SoA has been amended to only show the required assessments.

Trial Period	**Treatment Cycle =6 weeks**				**EOT**	**Posttreatment**			**Notes**
						Safety Follow-up[a]	**Follow-up[b]**	**Survival Follow-up**	
Visit Timing/ Cycle Number	**1[c]**	**2**	**3 to 9**	**>9 (lenvatinib only)**	**At DC**	**30 Days After Last Dose**	**Every 12 weeks**	**Every 12 weeks**	**All procedures are to be performed before administration of study intervention unless otherwise indicated**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Administrative and General Procedures									
Second Course informed consent obtained	X								New documented informed consent must be obtained before entering Second Course
Inclusion/exclusion criteria	X								
Concomitant medications	X	X	X	X	X	X	**X**		Prior medications need to be collected as detailed in Section 6.5.

Trial Period	**Treatment Cycle =6 weeks**				**EOT**	**Posttreatment**			**Notes**
						Safety Follow-up[a]	**Follow-up[b]**	**Survival Follow-up**	
Visit Timing/ Cycle Number	**1[c]**	**2**	**3 to 9**	**>9 (lenvatinib only)**	**At DC**	**30 Days After Last Dose**	**Every 12 weeks**	**Every 12 weeks**	**All procedures are to be performed before administration of study intervention unless otherwise indicated**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Study Intervention Administration									
Lenvatinib dispensed	X	X	X	X					Lenvatinib will be dispensed on Day 1 and Day 22 of every cycle. The decision to continue lenvatinib during SC will be at the discretion of the investigator. Lenvatinib treatment will continue until meeting at least 1 of the DC criteria listed in Section 7.1. Dose for lenvatinib at Second Course should not exceed the last tolerable dose during the Consolidation Phase.
Lenvatinib administration	<----------			---------->					Lenvatinib 20 mg orally qd.
Pembrolizumab administration	X	X	X						Pembrolizumab 400 mg IV Q6W. Participants who are eligible for SC may receive up to an additional 9 cycles of treatment with pembrolizumab.

Trial Period	Treatment Cycle =6 weeks				EOT	Posttreatment			Notes
						Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	
Visit Timing/ Cycle Number	1[c]	2	3 to 9	>9 (lenvatinib only)	At DC	30 Days After Last Dose	Every 12 weeks	Every 12 weeks	All procedures are to be performed before administration of study intervention unless otherwise indicated
Scheduling Window (days)	+3	±3	±3	±3		+7	±7	±14	
Efficacy Procedures									
Tumor imaging									SC baseline imaging should be performed within 28 days before SC C1. Perform imaging Q12W (84 ± 7 days) from SC C1. Schedule should be followed regardless of treatment delays. -If imaging was obtained within 4 weeks before DC, scan at DC is not mandatory. *Follow-up visits may be scheduled to coincide with Follow-up imaging. As of Amendment 8 on-study imaging is no longer required and should be performed per local standard of care.
Subsequent antineoplastic therapy status					X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
Survival status	<---------->							X	Participants may be contacted for survival status at any time during the course of the study.

Trial Period	Treatment Cycle =6 weeks				EOT	Posttreatment			Notes
						Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	
Visit Timing/ Cycle Number	**1[c]**	**2**	**3 to 9**	**>9 (lenvatinib only)**	**At DC**	**30 Days After Last Dose**	**Every 12 weeks**	**Every 12 weeks**	**All procedures are to be performed before administration of study intervention unless otherwise indicated**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Clinical Procedures/Assessments									
Adverse event monitoring	X	X	X	X	X	**X**	**X**		Will be assessed on Day 1 and Day 22 of every cycle. Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Telephone or virtual visit	X								At C1D8 only, to report blood pressure and record adverse events. Blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee.
Full physical examination	X				X				To be performed within 7 days before SC C1.
Directed physical examination		X	X	X		X			Will be assessed on Day 1 and Day 22 of every cycle.
Vital signs, weight	X	X	X	X	X	X			Vital signs must be taken in the clinic. Will be assessed on Day 1 and Day 22 of every cycle.

Trial Period	Treatment Cycle =6 weeks				EOT	Posttreatment			Notes
						Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	
Visit Timing/ Cycle Number	**1[c]**	**2**	**3 to 9**	**>9 (lenvatinib only)**	**At DC**	**30 Days After Last Dose**	**Every 12 weeks**	**Every 12 weeks**	**All procedures are to be performed before administration of study intervention unless otherwise indicated**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
12-lead ECG with QTc measurement	X		X	X	X	X			ECG is performed every other cycle in SC. For high-risk participants (as defined in Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up Visits. For country-specific requirements see Appendix 7.
ECOG performance status	X		X	X	X				Perform within 3 days before SC C1. ECOG is reviewed every other cycle in SC.
Laboratory Procedures/Assessments: Analysis Performed by Local Laboratory									
Pregnancy test (WOCBP only)	X	X	X	X	X	X			Will be assessed on Day 1 and Day 22 of every cycle. WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention and before each subsequent testing day as indicated. See Section 8.3.6.
CBC with Differential	X	X	X	X	X	X			Will be assessed on Day 1 of every Cycle.
Chemistry Panel	X	X	X	X	X	X			Perform within 10 days before SC C1. After SC C1, collect within 3 days before dosing. Will be assessed on Day 1 and Day 22 of every cycle.

Trial Period	Treatment Cycle =6 weeks				EOT	Posttreatment			Notes
						Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	
Visit Timing/ Cycle Number	**1[c]**	**2**	**3 to 9**	**>9 (lenvatinib only)**	**At DC**	**30 Days After Last Dose**	**Every 12 weeks**	**Every 12 weeks**	**All procedures are to be performed before administration of study intervention unless otherwise indicated**
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±14**	
Urine dipstick (Urinalysis)	X	X	X	X	X	X			Urine dipstick testing for protein will be performed within 3 days before Day 1 of every cycle while participants are taking lenvatinib. If lenvatinib is discontinued, urine dipstick is only required at EOT and Safety Follow-up Visits.
PT/INR and aPTT/PTT	X								Perform within 10 days before SC C1. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
Thyroid function (T3, T4, and TSH)	X*	X	X	X	X	X			*Thyroid function tests will be performed at C1 and then on Day 1 at every cycle thereafter. -Perform within 10 days before SC C1. After SC C1, collect within 3 days before dosing. -Participants may be dosed in subsequent cycles after SC C1 while thyroid function tests are pending. -May use central laboratory only if local laboratory is not capable.

AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta-human chorionic gonadotropin; CBC=complete blood count; CXDY=Cycle X Day Y; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FT4=free thyroxine; hr/H=hours; INR=international normalized ratio; PD=progressive disease; PT=prothrombin time; PTT=partial thromboplastin time; QXW=every X weeks; qd=once daily; QTc=corrected QT interval; SAE=serious adverse event; SC=Second Course; T3=triiodothyronine; T4=thyroxine;; TSH=thyroid-stimulating hormone; UA=urine analysis; WOCBP=woman of childbearing potential.

Note: Second Course will be for eligible participants from Part 1 and Part 2.

a. If DC Visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required.
b. For participants discontinuing SC for reasons other than PD, Follow-up Visits and imaging continue until PD or initiation of a new antineoplastic therapy. Participants discontinuing SC treatment with PD proceed directly to Survival Follow-up.
c. C1D1 procedures should be completed within 28 days of radiographic BICR verified disease progression.

2 INTRODUCTION

Gastric cancer remains a major health problem worldwide. Gastric cancer is the fifth most common cancer in the world and is a major cause of cancer-related death [Bray, F., et al 2018]. There were over 1 million new cases of gastric cancer worldwide in 2018 (683,754 men, 349,947 women). There were 783,000 deaths (513,555 men, 269,130 women), making it the third-leading cause of cancer death globally in both sexes [Bray, F., et al 2018]. Age-standardized incidence rates are about twice as high in men as in women. Gastric cancer incidence varies markedly by geographic region. More than 70% of cases occur in developing countries, and half the world total occurs in Eastern Asia. In the European Union, incidence and mortality for gastric cancer were estimated at 82,000 (51,000 in males and 31,000 in females) and 58,000 (35, 000 in males and 23,000 in females), respectively in 2012 [Ferlay, J., et al 2014]. In the United States, incidence and mortality estimated at 21,000 (13,000 in males and 8,000 in females) and 12,000 (7,000 in males and 5,000 in females), respectively in 2012 [Ferlay, J., et al 2014].

Although a subset of gastric cancers overexpress or amplify HER-2, ErbB2 and benefit from HER-2-targeted agents such as trastuzumab, the majority of gastric cancers (80% to 90%) are HER-2 negative [Bang, Y. J., et al 2010]. Promising activity with immunotherapy has been shown in recurrent, refractory gastric cancer, although the overall benefit of immunotherapy in gastric cancer has been modest, and the majority of patients succumb to their disease about 1 year after initial diagnosis [Fuchs, C. S., et al 2018] [Shitara, K., et al 2018] [Tabernero, J., et al 2019]. As such, new therapeutics, as well as novel combinations, are needed to improve outcomes. This study is designed to evaluate the safety and efficacy of combination therapy with lenvatinib (also known as E7080 or MK-7902), pembrolizumab, and chemotherapy as a first-line treatment in adult participants with advanced unresectable or metastatic HER-2 negative gastric cancer.

2.1 Study Rationale

This study will explore the potentially synergistic combination of lenvatinib and pembrolizumab with the standard and currently recommended preferred chemotherapy regimens for the treatment of advanced and metastatic gastric cancer. Chemotherapy doses will be limited to 4 cycles of CAPOX or 6 cycles of mFOLFOX6, which is a significant cumulative dose reduction compared with standard chemotherapy regimens and intended to control tumor burden and clinical disease during the Induction Phase. After discontinuation of chemotherapy, participants will continue lenvatinib and pembrolizumab for up to 2 years of total therapy. However, participants can continue lenvatinib beyond 2 years, at the investigator's discretion. This study design leverages data from known established treatment standards, as well as recently completed Phase 3 clinical studies and highly encouraging Phase 2 efficacy studies.

Lenvatinib in Combination with Pembrolizumab in Gastric Cancer

Lenvatinib in combination with pembrolizumab has been studied in an open-label Phase 2 study in first-line and second-line advanced gastric cancer. This study was a single arm study that included 29 participants treated with initial dose of lenvatinib 20 mg daily and

pembrolizumab 200 mg IV Q3W. The ORR was 69% (95% CI: 49, 85) with a DCR of 100% (95% CI: 88, 100), and a median PFS of 7.1 months (95%CI: 4.2, 10.0); the median OS was not reached. This response rate is remarkable considering the expected response rate of pembrolizumab monotherapy is 15% and <5% for lenvatinib, thus suggesting promising potential synergy with this combination therapy for advanced gastric cancer [Kawazoe, A., et al 2020].

With regard to safety, the combination therapy had manageable safety profiles. Reported Grade ≥3 TRAEs were hypertension (38%), proteinuria (17%), and platelet count decreased (7%). The majority of participants required a reduction of the initial lenvatinib 20-mg dose, with many participants showing a response at 14 mg and 10 mg dosing [Kawazoe, A., et al 2020].

The strategy to combine a PD-1 inhibitor with chemotherapy and VEGF TKI is being studied in a single arm Phase 2 study (currently ongoing; NCT03472365). In this study, camrelizumab (PD-1 inhibitor) was combined with capecitabine and oxaliplatin for 4 to 6 cycles followed by camrelizumab and apatinib (VEGF TKI). Of 46 evaluable participants, there was 1 CR, and 31 PR, for an ORR of 69.6% and DCR of 89.1%. Confirmed ORR was 58.7% and DCR was 78.3%. Overall, the treatment strategy was well tolerated with cutaneous reactive capillary endothelial proliferation (64.6%) and expected hematologic toxicities being most prevalent [Shen, L., et al 2019]. The skin toxicities described are likely attributed to camrelizumab and are not expected with pembrolizumab.

LEAP-005 is an ongoing Phase 2 study in advanced solid tumors for which there is a third line gastric cohort. In this study, the combination of lenvatinib and pembrolizumab has been shown to be safe and tolerable (MSD internal data).

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2.2 Background

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and 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 IV immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

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 CTLA-4 that has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

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

2.2.1.2 Lenvatinib

Angiogenesis, the formation of new blood vessels from a preexisting vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGFRs 1-3)

play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. and Hicklin, D. J. 2008] [Tammela, T. and Alitalo, K. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR, also play important roles in tumor angiogenesis [Cross, M. J. and Claesson-Welsh L. 2001] [Lieu, C., et al 2011] [Limaverde-Sousa, G., et al 2014].

Lenvatinib is a potent multiple RTKi that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), FGFR1-4, PDGFRα, c-KIT, and RET. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis.

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF derived and FGF-derived tube formation of HUVEC with IC_{50} values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10 mg/kg and 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib showed antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

In summary, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in HUVEC models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer drugs.

Lenvatinib has shown clinical efficacy in several tumor types. In the US, as of 2021, lenvatinib is indicated in the treatment of locally recurrent or metastatic progressive, radioactive iodine-refractory differentiated thyroid cancer, in combination with everolimus for advanced renal cell carcinoma after 1 prior antiangiogenic therapy, and for the first-line treatment of unresectable hepatocellular carcinoma (see lenvatinib package insert). In addition, as part of postmarketing request, the safety and efficacy of lenvatinib dosing was evaluated in 2 postmarketing studies in differentiated thyroid cancer and renal cell carcinoma respectively. In the DTC study, the lenvatinib dose of 18 mg/day failed to show noninferiority versus the approved lenvatinib 24 mg/day starting dose, as measured by ORR. In the RCC study, the lenvatinib dose of 14 mg/day failed to show noninferiority versus the approved 18 mg/day dose. These 2 studies suggest that maximizing the dose of lenvatinib may be important for best long-term outcomes[Brose, M. S., et al 2020] [Pal, S., et al 2020].

2.2.1.3 Lenvatinib Plus Pembrolizumab

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

In preclinical models, lenvatinib decreased the TAM population, which is known as an immune regulator in the tumor microenvironment. The decrease in TAM population was accompanied by increases in activated cytotoxic T-cell populations through stimulation of interferon-gamma signaling, resulting in increased immune activation[Kimura, T., et al 2018]. The immune modulating effect of lenvatinib may result in a potent combination effect with PD 1/L1 signal inhibitors.

The effect of combining lenvatinib with an antihuman PD-1 humanized mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared with control. In the RAG murine tumor isograft tumor model, survival in the group treated with the combination was significantly longer than that of the respective monotherapy groups. In the CT26 murine tumor isograft model, treatment with the combination significantly increased the population of activated cytotoxic T-cells compared with that of the respective monotherapy groups[Kato, Y., et al 2019]. All treatments were well tolerated and severe body weight loss was not observed.

There are a number of ongoing clinical studies investigating the combination of lenvatinib plus pembrolizumab in a variety of solid tumors in LEAP studies. Additionally, in KEYNOTE-146, a Phase 1b/2 study in participants with solid tumors, the lenvatinib and pembrolizumab combination was safe and tolerable, leading to US regulatory approval of the lenvatinib and pembrolizumab regimen for treatment of endometrial carcinoma. Based on safety data from these studies, it is anticipated that the combination of lenvatinib and pembrolizumab with chemotherapy will have an acceptable overlapping safety profile.

2.2.1.4 Chemotherapy

Despite a large number of randomized studies, there is no globally accepted standard first-line chemotherapy regimen in HER-2 negative, advanced, unresectable and/or metastatic gastric and GEJ adenocarcinoma. In general, combination chemotherapy regimens provide higher response rates than do single agents. Many patients are recommended to receive a fluoropyrimidine-platinum doublet over more toxic triplet chemotherapeutic regimens.

There is accumulating evidence demonstrating that chemotherapy agents including 5-FU and oxaliplatin that are frequently used to treat malignancies may modulate the intrinsic

immunogenicity of tumor and sensitize tumors to immunotherapy agents [Pfirschke, C., et al 2016] [Zhou, J., et al 2017]. Preclinical and clinical evidence suggest that conventional chemotherapies reactivate antitumor immune responses by increasing immunogenic cell death and antigen release, and/or by inhibiting immunosuppressive factors in the tumor microenvironment [Emens, L. A. and Middleton, G. 2015] [Galluzzi, L., et al 2015] [Vincent, J., et al 2010]. Further, chemotherapies can enhance tumor antigen presentation by upregulating the expression of tumor TCR themselves, or of the MHC1 molecules to which the TCRs bind [Emens, L. A. and Middleton, G. 2015].

The fluoropyrimidine/platinum doublet combination is a common first-line therapy for metastatic gastric cancer, and it is considered "preferred" by the NCCN Gastric Cancer Guideline committee [National Comprehensive Cancer Network 2020] [Smyth, E. C., et al 2016]. Fluoropyrimidine-platinum doublet regimens containing 5-FU or capecitabine and cisplatin or oxaliplatin are recognized worldwide as standard first-line chemotherapy regimens for patients with metastatic gastric and GEJ adenocarcinoma.

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

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

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

Most frequently used doublet regimens are XP, FP, CAPOX, and FOLFOX. Choices among these regimens are typically based on patients' general medical condition and comorbidities in consideration of the different toxicity profiles of the regimens as well as regional preferences. This practice pattern is supported by global consensus guidelines for treatment of advanced gastric cancer, which recommend use of any of the doublet regimen discussed above [National Comprehensive Cancer Network 2020] [Cunningham, D., et al 2008].

FOLFOX and CAPOX have been studied extensively in advanced gastric cancer and are routinely used in clinical practice globally. In general, FOLFOX and CAPOX are expected to have a similar profile of adverse events, with the most common adverse events being gastrointestinal (ie, diarrhea, nausea, vomiting and stomatitis) and neurosensory toxicities (ie, paresthesia and peripheral neuropathy). However, there are differences between the rates at which key events may occur. FOLFOX is anticipated to be associated with more Grade 3/4

neutropenia and febrile neutropenia than CAPOX. Conversely, CAPOX is expected to be associated with more hand-foot syndrome and diarrhea. Rates of Grade 3/4 neurosensory toxicity and cardiac disorders are anticipated to be similar [Cassidy, J., et al 2011]. In summary, these 2 regimens are expected to have similar efficacy and will allow investigators a choice based on each participant's medical condition.

2.2.1.5 Lenvatinib in Combination With Chemotherapy in Other Indications

In the ongoing Phase 3 LEAP-006 study, which is a randomized, double-blind study of first-line pembrolizumab plus platinum doublet chemotherapy (pemetrexed and platinum) +/- lenvatinib (8 mg qd) in participants with metastatic NSCLC (NCT 03829319) [Hui, R., et al 2019]. The Safety Run-in (Part 1) portion of this study is complete, and this regimen was generally tolerable.

In an ongoing study of patients with rectal cancer, the first 9 participants have received up to 24 mg qd lenvatinib plus capecitabine (800 mg/m^2 BID) and it was well tolerated [Frakes, J., et al 2019].

2.2.2 Preclinical and Clinical Studies

Preclinical studies for lenvatinib and pembrolizumab are described in the respective IBs.

2.2.2.1 Clinical Activity of Pembrolizumab in Advanced Gastric Cancer

Immune checkpoint inhibitors such as pembrolizumab have showed durable immune-mediated antitumor activity in participants with advanced gastric cancer. Clinical proof of concept for pembrolizumab in these participants was shown in Cohort D of the Phase 1b study, KEYNOTE-012, which enrolled 39 participants with gastric or GEJ tumors expressing PD-L1 assessed using a prototype PD-L1 IHC assay [Muro, K., et al 2016]. Eight of 39 participants had an OR by RECIST 1.1 using central radiologic review for an ORR of 22% (95% CI: 10, 39).

The Phase 2 study, KEYNOTE-059, tested pembrolizumab monotherapy in a larger cohort (Cohort 1) of participants whose tumors had progressed on 2 or more lines of systemic therapy (third line + participants). In this study, pembrolizumab monotherapy showed clinically meaningful ORR in this heavily treated population for whom there are no other effective agents. Durable objective responses were observed in the all-comer population regardless of PD-L1 status with ORR of 12%, while a higher response rate (16%) was observed in the PD-L1 positive population [Wainberg, Z. A., et al 2017]. Based on data from KEYNOTE-059, pembrolizumab received accelerated approval by the US FDA in September 2017 for treatment of third line plus participants with tumors expressing PD-L1 (CPS ≥1) assessed by an FDA-approved test. KEYNOTE-059 included 2 additional cohorts where pembrolizumab was tested in first-line gastric cancer participants either as monotherapy (Cohort 3) or in combination with a fluoropyrimidine and cisplatin (Cohort 2). Cohort 3 enrolled 31 participants whose tumors expressed PD-L1 (CPS ≥1). Cohort 2 enrolled participants irrespective of PD-L1 expression (all-comers). In both cohorts, ORR was assessed according to RECIST 1.1 by independent central radiological review. The combination of pembrolizumab with cisplatin and 5-FU or capecitabine in Cohort 2 (n=25)

yielded an ORR of 60% (95% CI: 39%, 79%) and a DCR of 80% (95% CI: 59%, 93%). Responses were observed regardless of PD-L1 status. Median OS in Cohort 2 was 13.8 months (95% CI: 8.6, NR). Monotherapy in PD-L1 positive first-line participants (Cohort 3) yielded an ORR of 26% (95% CI: 12, 45); median OS was 20.7 months (95% CI; 9.2, 20.7) [Fuchs, C. S., et al 2018].

KEYNOTE-061 (NCT02370498) was a global Phase 3 study of pembrolizumab versus paclitaxel for previously treated advanced gastric/GEJ cancer. Pembrolizumab reduced the risk of death by 18% versus paclitaxel in participants with PD-L1 CPS ≥1, although this difference was not statistically significant. Durable benefit of pembrolizumab was shown in this study. After a median follow-up of 8 months, 7.8% of participants completed or remained on pembrolizumab, versus 0% with paclitaxel. Median OS was 9.1 months with pembrolizumab versus 8.3 months with paclitaxel; the difference did not reach statistical significance (HR 0.82, one-sided p=0.042). Twelve-month OS rates were 39.8% with pembrolizumab versus 27.1% with paclitaxel; 18-month OS rates were 25.7% versus 14.8%, respectively. There was no difference in PFS or ORR, but pembrolizumab responses were more durable: median duration of response was 18 months and 5.2 months for pembrolizumab and paclitaxel, respectively [Shitara, K., et al 2018].

KEYNOTE-062 (NCT02494583) was a global Phase 3 study of pembrolizumab as first-line monotherapy and combination therapy versus SOC chemotherapy (at the time of the study) for advanced gastric or GEJ adenocarcinoma. In this study, in participants with CPS ≥1, the OS for pembrolizumab monotherapy was found to be noninferior compared with chemotherapy with a median OS of 10.6 months (95% CI: 7.7, 13.8) compared with 11.1 months (95% CI: 9.2, 12.8) with an HR of 0.91 (95% CI: 0.69, 1.18). In participants selected for CPS ≥10, participants treated with pembrolizumab monotherapy showed an improved median OS of 17.4 months (95% CI: 9.1, 23.1) compared with 10.8 months (95% CI: 8.5, 13.8) HR of 0.69 (95% CI: 0.49, 0.97) with chemotherapy, although not formally tested based on the study statistical design. When pembrolizumab was combined with chemotherapy, the effect was more modest showing a 12.5 month (95% CI: 10.8, 13.9) median OS compared with 11.1 month (95% CI: 9.2, 12.8) with an HR 0.85 (95% CI: 0.70, 1.03) in participants with CPS ≥1. Similarly, in the CPS ≥10 selected participants the median OS for pembrolizumab combined with chemotherapy was 12.3 months (95% CI: 9.5, 14.8) compared with 10.8 months (95% CI: 8.5, 13.8) with an HR of 0.85 (95% CI: 0.62,1.17). Although these differences were not significant, pembrolizumab responses were more durable [Tabernero, J., et al 2019].

Taken together, the data show that pembrolizumab showed durable clinical benefit and favorable tolerability in advanced gastric cancer populations. In the context of the proposed study, it is important to note that pembrolizumab was safe in combination with chemotherapy, and it has showed promising activity, particularly in subsets of PD-L1 selected participants.

2.2.2.2 Clinical Activity of Pembrolizumab in Combination Therapy

Results from clinical studies combining PD-L1 agents and chemotherapies have had variable outcomes. These studies have showed that chemotherapies can be safely combined with PD-

L1 agents and many of them have showed promising anticancer activity [Gadgeel, S., et al 2016] [Gadgeel, S., et al 2020] [Wallin, J. J., et al 2016] [Wallin, J., et al 2016]. Various chemotherapies were combined with pembrolizumab and produced promising activity. In KEYNOTE-189, addition of pembrolizumab to pemetrexed and a platinum-based drug with first-line metastatic nonsquamous NSCLC showed significantly longer OS and PFS compared with placebo in combination with pemetrexed and a platinum-based drug [Gadgeel, S., et al 2020]. In colorectal cancer, FOLFOX plus bevacizumab was combined with atezolizumab and showed an acceptable safety profile and promising activity (ORR, 52%; median PFS, 14.1 months; DOR, 11.4 months) [Wallin, J., et al 2016]. In this study, there was a clear demonstration of increased PD-L1 expression, enhanced intra tumoral infiltration of CD8+ T-cells, and upregulation of an immune gene signature in tumor by use of FOLFOX alone or in combination with atezolizumab [Wallin, J., et al 2016]. Further, there was an association between an increase in immune gene signature and durability of clinical benefit.

2.2.2.3 Clinical Activity of VEGF TKI in Gastric Cancer

VEGF is a potent angiogenic factor which is upregulated in many tumors and is a marker for gastric cancer. VEGF levels are elevated in the presence of gastric cancer and decrease after tumor regression suggesting that VEGF levels could be a predictor of recurrence. In addition, high VEGF levels were correlated with poor prognosis and lower survival rates [Macedo, F., et al 2017].

When evaluated as monotherapy, the activity of VEGF TKI is modest in gastric cancer, although there appears to be some improvement in PFS and OS rates when compared with placebo. The ORR after treatment with sunitinib, sorafenib, apatinib, regorafenib, and ramucirumab ranged between 2.6% to 3.0%. However, in clinical studies with apatinib, regorafenib, and ramucirumab for which there was a placebo control, there was trend toward improvement in PFS and OS [Bang, Y. J., et al 2011] [Janjigian, Y. Y., et al 2015] [Li, J., et al 2016] [Pavlakis, N., et al 2016] [Fuchs, C. S., et al 2014]. When VEGF TKI were used in combination therapy, one study showed that the combination of ramucirumab and paclitaxel resulted in ORR 28%, and PFS of 9.6 months compared with 7.4 months for paclitaxel (HR: 0.807) leading to a new SOC option for second-line gastric cancer [Wilke, H., et al 2014]. Lenvatinib, as a multi-targeted VEGF TKI has been evaluated as monotherapy in a subset of gastric cancer participants in the Phase 1 study of advanced solid tumors. Of the 6 participants with advanced gastric cancer, there were no responders suggesting that combination therapy with lenvatinib is required for maximum efficacy and potential synergy [Boss, D. S., et al 2012].

2.2.3 Ongoing Clinical Studies

Several clinical studies involving pembrolizumab are currently ongoing in participants with gastric/GEJ cancer as presented in Table 1.

Table 1 Ongoing Clinical Studies With Pembrolizumab in Gastric Cancer

Study	Phase	Study Population	Study Intervention
KN-585	3	Previously untreated, locally advanced resectable gastric or GEJ adenocarcinoma	Pembrolizumab plus chemotherapy *versus* Placebo plus chemotherapy
KN-811	3	HER-2 positive with advanced gastric or GEJ adenocarcinoma	Pembrolizumab plus trastuzumab plus chemotherapy *versus* Placebo plus trastuzumab plus chemotherapy
KN-859	3	Previously untreated, HER-2 negative, advanced gastric or GEJ adenocarcinoma	Pembrolizumab plus chemotherapy *versus* Placebo plus chemotherapy
LEAP-005	2	Relapsed/refractory TNBC, ovarian cancer, gastric cancer, colorectal cancer, GBM, or biliary tract cancers	Open-label lenvatinib plus pembrolizumab
KN-659	2b	First-line participants with advanced gastric/GEJ tumor	Nonrandomized SOX + pembrolizumab or SP + pembrolizumab.
KN-059	2	Recurrent or metastatic gastric or GEJ adenocarcinoma	Pembrolizumab monotherapy *or* Pembrolizumab with cisplatin+5-fluorouracil
KN-061	3	Advanced gastric or GEJ adenocarcinoma who progressed after first-line therapy with platinum and fluoropyrimidine	Pembrolizumab *Versus* Paclitaxel
KN-062	3	Advanced Gastric or GEJ Adenocarcinoma	Pembrolizumab monotherapy *or* Pembrolizumab in combination with cisplatin+5-fluorouracil *versus* Placebo+cisplatin+5-fluorouracil
KN-063	3	Asian participants with advanced gastric or GEJ adenocarcinoma who progressed after first-line therapy with platinum and fluoropyrimidine	Pembrolizumab *Versus* Paclitaxel

GBM=glioblastoma; GEJ=gastroesophageal junction; HER-2=human epidermal growth factor receptor 2; KN=KEYNOTE; SOX=s1 oxaliplatin; SP=s1 cisplatin; TNBC=triple negative breast cancer

2.3 Benefit/Risk Assessment

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

Proposed study-specific benefits of the treatment combination of lenvatinib/pembrolizumab include:

- The potential for improved PFS/OS
- The potential for decreased cytotoxic side effects due to the reduced cumulative exposure to cytotoxic chemotherapy.

Proposed study-specific risks of the treatment combination of lenvatinib/pembrolizumab include:

- Mean decreased survival due to shorter duration of exposure to chemotherapy
- Additional toxicities from the addition of lenvatinib and/or pembrolizumab to chemotherapy regimen
- Lenvatinib and/or pembrolizumab specific side effects
- Unanticipated side effects

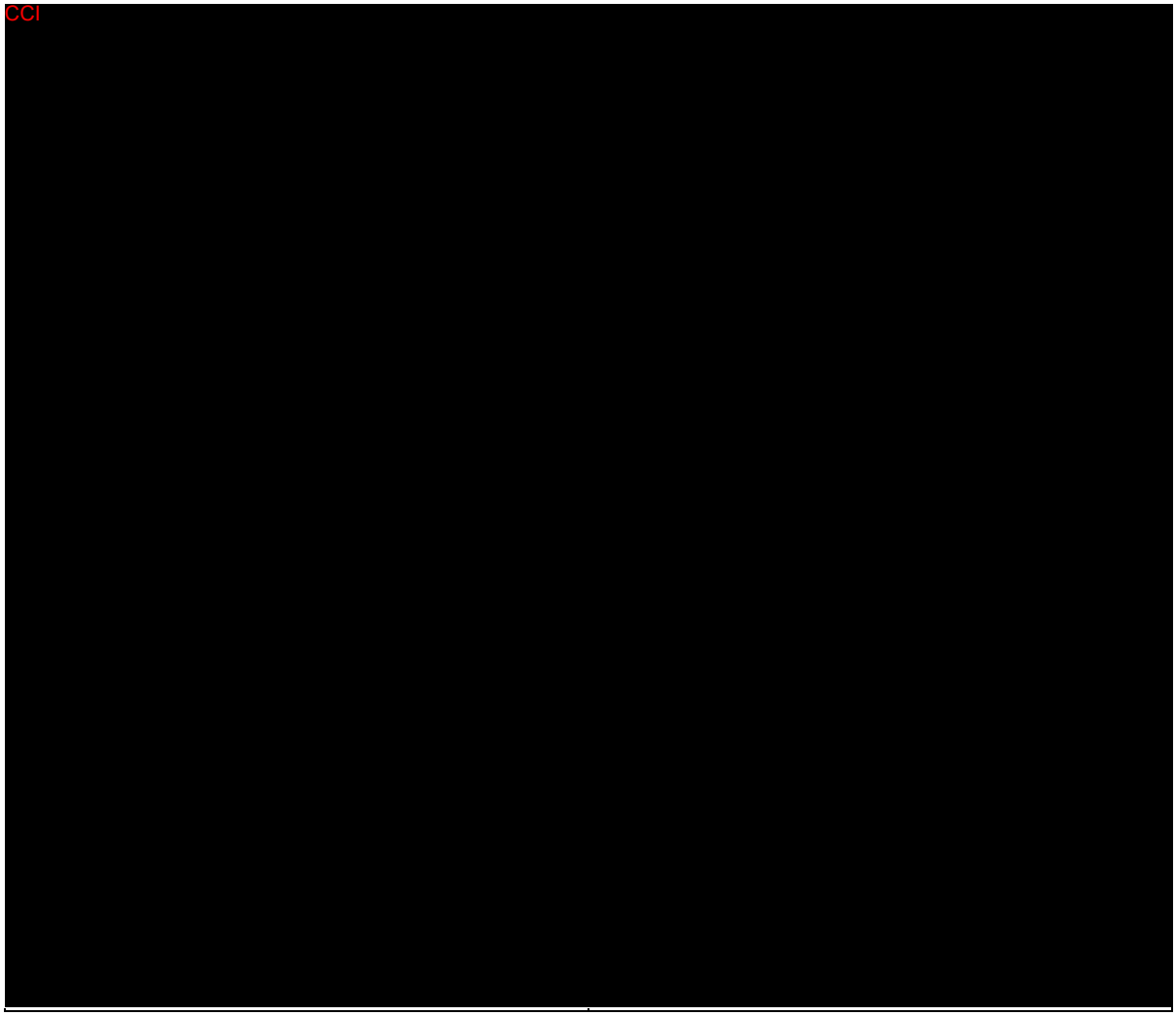
Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Male and female adults, at least 18 years of age with previously untreated, locally advanced unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma will be enrolled, and the following objectives and endpoints will be assessed (there are dual primary endpoints):

Primary Objective	**Primary Endpoint**
- Objective (Part 1): To evaluate the safety and tolerability of treatment with lenvatinib plus pembrolizumab plus chemotherapy.	- Dose-limiting toxicities, adverse events and study intervention discontinuations due to adverse events.
- Objective (Part 2): To compare the overall survival between treatment groups CCI	- Overall Survival: The time from randomization to death due to any cause
- Objective (Part 2): To compare the PFS between treatment groups CCI	CCI

Secondary Objectives	Secondary Endpoints
- Objective (Part 2): To compare ORR between treatment groups.	- Objective Response: Complete response or partial response
CCI [redacted]	
- Objective (Part 2): To estimate DOR, per RECIST 1.1 as assessed by BICR for each treatment group in participants with programmed cell death ligand 1 combined positive score ≥1 and in all participants.	- Duration of Response: The time from first response (complete response or partial response) to subsequent disease progression, or death from any cause, whichever occurs first
- Objective (Part 2): To evaluate the safety and tolerability of lenvatinib plus pembrolizumab plus chemotherapy versus chemotherapy	- Adverse events - Study intervention discontinuation due to adverse events
CCI [redacted]	



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

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active-controlled, parallel-group, multisite, open-label, study of lenvatinib plus pembrolizumab plus chemotherapy compared with chemotherapy only in participants with locally advanced unresectable/metastatic gastroesophageal adenocarcinoma.

There will be 2 parts to the study: a Safety Run-in (Part 1) and the Main Study (Part 2). In Part 1 (Safety Run-in), approximately 12 participants will be treated with lenvatinib in combination with pembrolizumab and chemotherapy (CAPOX or mFOLFOX6) to ensure that ~6 participants will be treated with lenvatinib in combination with pembrolizumab, capecitabine, and oxaliplatin (CAPOX), and ~6 participants will be treated with lenvatinib in combination with pembrolizumab, 5-FU, Leucovorin, and oxaliplatin (mFOLFOX6). Participants will be closely followed for unacceptable toxicities for 21 days after the first dose of study intervention (the DLT evaluation period) for the occurrence of specific AEs that are deemed dose limiting according to Table 2. If 3 or more DLTs occur in either oxaliplatin-containing cohort during this Safety Run-in, enrollment to Part 2 may be delayed to further examine safety data and consider study design changes. Participants in Part 1 will continue to receive study intervention and be followed in the posttreatment period as applicable. Safety Run-in data will be evaluated before enrollment for Part 2 commences. Participants in the Safety Run-in will be treated with full study treatment per SoA, which includes induction, consolidation and follow-up. Safety Run-in participants will not be included in the efficacy/safety analysis of randomized portion of the study (Part 2).

Table 2 Dose-Limiting Toxicities

Toxicity Category	Toxicity CTCAE Grade
Hematologic	Grade 4 neutropenia lasting for ≥7 days Grade 3 or Grade 4 febrile neutropenia[a] Grade 3 thrombocytopenia with bleeding; Grade 4 thrombocytopenia Grade 4 anemia
Other nonhematologic toxicity	Any other Grade 4 or a Grade 5 toxicity Grade 3 toxicities lasting >3 days excluding: ○ Nausea, vomiting, and diarrhea controlled by medical intervention within 72 hours ○ Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab Grade 3 hypertension not able to be controlled by medication Grade 3 or above gastrointestinal perforation Grade 3 or above wound dehiscence requiring medical or surgical intervention Any grade thromboembolic event
	Any Grade 3 nonhematologic laboratory value if: Medical intervention is required to treat the participant, or The abnormality leads to hospitalization

Toxicity Category	Toxicity CTCAE Grade
ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events v5.0. a Febrile neutropenia Grade 3 or Grade 4 • Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than 1 hour. • Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.	

In Part 2, approximately 878 eligible participants (not to include those participating in Part 1) with be randomly assigned in a 1:1 ratio to one of the following treatment arms:

1. Induction with lenvatinib 8 mg qd plus pembrolizumab (400 mg Q6W for 2 cycles) plus chemotherapy (CAPOX or mFOLFOX6) followed by consolidation with lenvatinib 20 mg qd plus pembrolizumab (400 mg Q6W for 16 cycles)

2. Chemotherapy only (control arm):

    - CAPOX Q3W: capecitabine 1000 mg/m^2 BID for 14 days (oral) and oxaliplatin 130 mg/m^2 (IV)

      OR

    - mFOLFOX6 Q2W: oxaliplatin 85 mg/m^2 (IV), 5-FU 400 mg/m^2 (bolus IV) plus 2400 mg/m^2 (continuous IV), and leucovorin 400mg/m^2 (IV) or levoleucovorin 200 mg/m^2 (IV)

CCI

[redacted]

Note: As of Amendment 8, participants who either completed lenvatinib plus pembrolizumab or chemotherapy administration or discontinued lenvatinib plus pembrolizumab or chemotherapy will discontinue from the study following the Safety Follow-up visit (Section 8.11.5.1). AE, SAE, and other reportable safety events will be reported and followed as described under Section 8.4. All participants in Efficacy Follow-up prior to initiation of Amendment 8 will stop efficacy assessments and be discontinued from the study and should continue with tumor imaging per local standard of care. All participants in Survival Follow-up prior to initiation of Amendment 8 are considered to have completed the study and should have a final survival contact; these participants will no longer be contacted for survival information.

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

The study design is depicted in Figure 1 (Safety Run-in), Figure 2 (Main Study) and Figure 3 (Second Course Treatment Phase).

In Part 2, this study will use a group sequential design, using an eDMC to monitor safety and efficacy during the course of the study. CCI [redacted]

Participants treated with pembrolizumab who complete 18 cycles (2 years) of treatment with SD or better, or participants who attain an investigator-determined CR and have received at least 4 cycles of pembrolizumab may be eligible for retreatment with up to an additional 9 cycles (approximately 1 year) of pembrolizumab if they experience radiographic disease progression confirmed by BICR after stopping treatment in the initial treatment phase. This retreatment is termed the Second Course Treatment Phase and is only available if the study remains open and the participant meets the criteria specified in Section 7.1. The decision of whether to continue lenvatinib treatment during the Second Course Treatment Phase will be at the discretion of the investigator. If continued, participants will be retreated at the same dose level and frequency as when they last received the combination of lenvatinib plus pembrolizumab. **Note: As of Amendment 8, Second Course will no longer be offered**. Any participant receiving Second Course retreatment prior to the initiation of Amendment 8 will be able to continue treatment as planned.

After the final analysis, participants may be transitioned to an extension study, if available.

4.2 Scientific Rationale for Study Design

Study and scientific rationale are described in Section 2.1.

4.2.1 Rationale for Endpoints

CCI [redacted]

CCI

[redacted]

RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility (Section 8.1.2). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional details.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer 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. AEs will be assessed as defined by CTCAE, Version 5.0.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

4.2.2 Rationale for Use of CAPOX and mFOLFOX6

Systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer as evidenced by treatment guidelines issued by the NCCN and ESMO [National Comprehensive Cancer Network 2020] [Smyth, E. C., et al 2016].

Despite a large number of randomized studies, there is no globally accepted standard first-line chemotherapy regimen in HER-2 negative, advanced, unresectable and/or metastatic gastric and GEJ adenocarcinoma. In general, combination chemotherapy regimens provide higher response rates than do single agents. Many patients are recommended to receive a fluoropyrimidine-platinum doublet over more toxic triplet chemotherapeutic regimens.

Platinum/fluoropyrimidine doublet regimens containing cisplatin or oxaliplatin and 5-FU or capecitabine are recognized worldwide as first-line chemotherapy regimens for advanced, unresectable, and/or metastatic gastric and GEJ adenocarcinoma. These platinum/fluoropyrimidine doublet regimens are considered “preferred” by the NCCN Gastric Cancer Guideline committee [National Comprehensive Cancer Network 2020].

Most frequently used doublet regimens are XP, FP, CAPOX, and FOLFOX. Choices among these regimens are based on a patient’s general medical condition and comorbidities in consideration of the different toxicity profiles of the regimens. This practice pattern is supported by global consensus guidelines regarding the treatment of advanced gastric cancer, which recommend use of any of the doublets discussed above [National Comprehensive Cancer Network 2020] [Smyth, E. C., et al 2016].

The current study will use CAPOX or mFOLFOX6 as the chemotherapy backbone regimens. Investigators will have a choice between CAPOX and mFOLFOX6. Use of infusional 5-FU in this study provides an alternative fluoropyrimidine treatment to those participants unable to take oral capecitabine.

4.3 Justification for Dose

4.3.1 Pembrolizumab

Based on the totality of data generated in the KEYTRUDA® development program, 200 mg Q3W is considered the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type.

The planned dose of pembrolizumab for this study is 400 mg Q6W [Lala, M., et al 2020]. This regimen has been approved by US FDA, across all adult indications, including monotherapy and combination therapy. A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala, M., et al 2018]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on M&S analyses, given the following rationale:

PK simulations demonstrating that in terms of pembrolizumab exposures:

- C_{avg} (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

- C_{min} at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.

- C_{max} at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.

- Exposure-response for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

Safety at the Q6W dosing schedule was bridged based on an established exposure-safety analysis anchored on the maximum clinically administered and well tolerated dose (10 mg/kg Q2W). The safety of pembrolizumab at doses of 2 mg/kg Q3W and 10 mg/kg Q3W in combination with chemotherapy was assessed in KEYNOTE-021 Cohorts A, B, and C in NSCLC participants. Based on limited data from approximately 37 participants at each dose level, the frequency of various AE categories was generally consistent between pembrolizumab 2 mg/kg Q3W in combination with chemotherapy and pembrolizumab 10 mg/kg Q3W in combination with chemotherapy, and no new safety concerns were identified in these cohorts. Because exposures of 400 mg Q6W fall within the range of exposures between 2 and 10 mg/kg Q3W, the safety profile of pembrolizumab 400 mg Q6W dose in

combination with chemotherapy is expected to be consistent with the safety of pembrolizumab 200 mg Q3W dose in combination with chemotherapy.

4.3.2 Lenvatinib

In this protocol, lenvatinib at 8 mg daily dose will be combined with pembrolizumab and either CAPOX or mFOLFOX6. Lenvatinib has been studied in combination with chemotherapy in NSCLC. In the Phase 1 dose-escalation study, lenvatinib was combined with paclitaxel (200 mg/m2) followed by 1-hour infusion of carboplatin (AUC 6.0 min mg/mL). Twenty-eight patients were treated for which there were 2 DLTs. A MTD was defined as 4 mg BID (equivalent to 8 mg daily). Even at the 4 mg BID dosing, efficacy remained impressive with an ORR 68.2% (95% CI 45.1-86.1), and DCR of 90.9% (95% CI 70.8-98.9) [Nishio, M., et al 2013].

LEAP-006 is an ongoing Phase 3, randomized, double-blind study of first-line pembrolizumab plus platinum doublet chemotherapy (pemetrexed and platinum) +/- lenvatinib (8 mg qd) in participants with metastatic NSCLC. In this study, the regimen was tolerable with fewer than 3 DLTs occurring in each platinum-containing arm. The ORR was 69.2% [Nishio, M., et al 2020]. Part 2 randomized portion of the study is ongoing. Based on the data from the LEAP-006 study, 8 mg is likely to be safe and effective when used in combination with pembrolizumab and chemotherapy.

During the Consolidation Phase, lenvatinib at 20 mg oral daily will be given in combination with pembrolizumab without chemotherapy. In the KEYNOTE-146/Study 111 (NCT02501096) Phase 1b/2 study of lenvatinib plus pembrolizumab in solid tumors, TRAEs were reported in 97% of patients. Treatment-related AEs resulted in lenvatinib dose reduction and/or interruption in 85%, lenvatinib discontinuation in 13%, pembrolizumab dose interruption (45%) and pembrolizumab discontinuation (15%). The most common AEs reported as reasons for lenvatinib dose reduction and/or interruption were fatigue (26%), diarrhea (23%), hypertension (17%), decreased appetite (16%), and proteinuria (11%) [Taylor, M. H., et al 2020].

In an open-label Phase 1b/2 study of lenvatinib plus pembrolizumab in participants with advanced gastric cancer many patients were treated with the combination therapy at 20 mg daily dose of lenvatinib. TRAE led to dose interruptions in 28 patients (97%) and at least 1 dose reduction of lenvatinib in 29 patients (100%); 1 level dose reduction (14 mg) in 9 patients (31%), 2 level (10 mg) in 14 patients (48%), 3 level (8 mg) in 5 patients (17%) and 4 level (4 mg) in 1 patient (3%) [Kawazoe, A., et al 2020a]. As described in the background, noninferiority of lower dose lenvatinib has been studied in approved indications of DTC and RCC, showing that lower dosages of lenvatinib have failed to show noninferiority to higher approved dosing. These studies suggest that maximizing the dose of lenvatinib may be important for best long-term outcomes [Brose, M. S., et al 2020] [Pal, S., et al 2020]. Based on these data, during Consolidation Phase, the starting dose of lenvatinib will be 20 mg oral daily combined with pembrolizumab 400 mg every 6 weeks. Dose escalation schema in this study is defined such that only patients who tolerate 8-mg dose during induction would be eligible to escalate the lenvatinib dose. We expect that some participants will subsequently

need dose reduction due to toxicity but understand that maximizing the lenvatinib the dose may confer better long-term outcomes.

A 21-day Safety Run-in in Part 1 will include approximately 12 participants, and these participants will start on an 8 mg dose of lenvatinib (see Section 4.1 for details). For those participants who do not tolerate 8 mg during the Induction Phase or 20 mg during the Consolidation Phase due to severe hypersensitivity and/or Grade 3 or higher ongoing AEs, dose reduction/discontinuation/dose escalation/dose reescalation will occur as described in detail in Section 6.6.3.

4.3.3 Maximum Dose/Exposure of Lenvatinib and Pembrolizumab for This Study

The maximum dose/exposure of lenvatinib in this study is lenvatinib 8 mg qd for 12 weeks in the Induction Phase, followed by lenvatinib 20 mg qd during the Consolidation Phase for up to 2 years. The maximum dose/exposure of pembrolizumab allowed in this study is 400 mg Q6W for 18 infusions in the First Course (approximately 2 years), and 9 infusions (approximately 1 year) in the Second Course.

Participants may continue treatment with lenvatinib if they experience clinical benefit according to the PI with Sponsor consultation until disease progression or unacceptable toxicity.

4.3.4 Background Chemotherapy

Participants randomized to the lenvatinib plus pembrolizumab plus chemotherapy arm will receive either 4 cycles of CAPOX OR 6 cycles of mFOLFOX6 given concurrently with lenvatinib and pembrolizumab concurrently during the Induction Phase. Participants randomized to this treatment arm will receive lenvatinib and pembrolizumab in the Consolidation Phase unless either drug is discontinued according to dose modification criteria due to AEs. Participants will NOT receive chemotherapy during the Consolidation Phase if randomized to this arm of therapy. Participants who are randomized to the chemotherapy arm will continue chemotherapy with either CAPOX or mFOLFOX6 per local SOC, consistent with NCCN guidelines for the treatment of first-line advanced/metastatic gastric cancer. The decision to treat with CAPOX or mFOLFOX6 is per investigator judgment and made on a participant-by-participant basis. For any treatment regimen, once the participant is randomized, the chemotherapy (backbone) cannot be changed. Country-specific requirements are noted in Appendix 7.

4.3.4.1 CAPOX

Dose determination for capecitabine and oxaliplatin in the CAPOX regimen is in accordance with prescribing information for gastric cancer as described in their package inserts.

In this protocol, the dose regimen will be oxaliplatin (130 mg/m2 IV) on Day 1 and Day 22 of each treatment cycle plus capecitabine (1000 mg/m2 orally twice daily) on Days 1 to 14, and Days 22 to 35 of each treatment cycle (Q3W).

The combination of capecitabine, oxaliplatin, and pembrolizumab is currently being evaluated in an investigator-initiated study in the United States. This study is a single arm, Phase 2 study investigating the combination of pembrolizumab, oxaliplatin, and capecitabine in the first-line treatment of metastatic/recurrent adenocarcinoma of the esophagus or stomach and is being conducted at Duke University (KeyLargo study). Enrollment began in January 2018. The doses of capecitabine, oxaliplatin, and pembrolizumab used are identical to those used in this protocol.

4.3.4.2 mFOLFOX6

Dose determination for oxaliplatin, leucovorin, 5-FU in the mFOLFOX6 regimen is in accordance with prescribing information for gastric cancer as described in their package inserts.

In this protocol, the dose regimen will be oxaliplatin (85 mg/m2 IV) plus leucovorin 400 mg/m2 IV) plus 5-FU (400 mg/m2) IV bolus and 5-FU (2400 mg/m2) IV on Day 1 of each chemotherapy cycle (Q2W).

The choice of the platinum agent used for treatment for gastric cancer in first-line therapy has changed during the last 2 to 3 years in the Group of 7 countries (US, Germany, UK, France, Spain, Italy, Japan) and other countries. Oxaliplatin combinations are now the broad SOC in most countries (mFOLFOX6: 5-FU plus oxaliplatin plus leucovorin), moving away from the nephrotoxicity of cisplatin-based regimens (predominantly cisplatin + 5-FU). The advantages of mFOLFOX6 regimen include elimination of several hours of IV hydration needed to avoid cisplatin nephrotoxicity, and less nausea, vomiting, thromboembolic events and anemia. The SOC chemotherapy predominantly used in the US is mFOLFOX6 (leucovorin plus 5-FU plus oxaliplatin) in first-line gastric cancer.

In a Phase 2 study (HCRN GI14-186), pembrolizumab has been combined with mFOLFOX6 in colorectal cancer using the dose regimen described in this current protocol and was found to show tolerable toxicity. The rate of Grade 3/4 toxicity associated with mFOLFOX6/pembrolizumab was 36.7%. No Grade 5 toxicity was seen on study. The DMC recommended modification of the chemotherapy regimen to oxaliplatin 68 mg/m2, leucovorin 400 mg/m2, 5-FU 320 mg/m2, 5-FU infusion of 1920 mg/m2 over 46 hours based on initial findings that suggested increased neutropenia [Shahda, S., et al 2017].

However, in a subsequent KEYNOTE-651 study, investigating pembrolizumab plus mFOLFOX (Cohort B) in participants with metastatic colorectal cancer, the same regimen without any dose reduction was determined to be safe and tolerable, with the most common Grade 3 TRAEs being anemia and neutrophil count decreased (13% each) [Kim, R., et al 2019].

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor

receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be 5 years (~1 year after study intervention has been completed) to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has histologically and/or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic gastroesophageal adenocarcinoma.

   Note: Participants who are eligible for radiotherapy or neoadjuvant therapy are not eligible.

2. Is not expected to require tumor resection during the treatment course.

3. Has gastroesophageal adenocarcinoma that is not HER-2/neu positive.

   Note: Participants with gastroesophageal adenocarcinoma that is known to be HER-2/neu positive are not eligible. If HER-2/neu status is unknown, site should follow local standards if HER-2/neu testing is required as SOC.

   Country-specific requirements are provided in Appendix 7.

4. Has measurable disease as defined by RECIST 1.1 by scan with IV contrast as determined by the local site investigator. Lesions situated in a previously irradiated area are considered measurable if progression has been showed in such lesions since the completion of radiation (by scans with contrast).

Demographics

5. Is male or female at least 18 years of age inclusive at the time of signing the informed consent.

Male Participants

6. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after last dose of lenvatinib or 90 days after last dose of chemotherapy, whichever comes last:

- Refrain from donating sperm

  PLUS either:

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

  OR

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

- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Please note that 7 days after lenvatinib is stopped, if the participant is on pembrolizumab only, no male contraception measures are needed.

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

Country-specific requirements are listed in Appendix 7.

Female Participants

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

- Is not a WOCBP

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period through 120 days after last dose of pembrolizumab, 30 days after last dose of lenvatinib, or 180 days after last dose of chemotherapy, whichever occurs last, or not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours for urine or 72 hours for serum before the first dose of study intervention.

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

- Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.

- Abstains from breastfeeding during the study intervention period and for at least 120 days after pembrolizumab or 30 days after cessation of lenvatinib, or 180 days after chemotherapy, whichever occurs last.

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

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

Informed Consent

8. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study.

Additional Categories

9. Has a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior to the first dose of study treatment.

10. Has provided a tumor tissue sample for PD-L1 and MSI biomarker analysis. If the initial tissue is inadequate for the analysis, an additional specimen will need to be provided.

11. Has adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg and no change in antihypertensive medications within 1 week prior to randomization.

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

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500 /mcL
Platelets	≥100,000 /mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]
Renal	
Calculated[b] creatinine clearance	≥50 mL/min
Hepatic	
Total bilirubin	≤1.5 X ULN **OR** Direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN **OR** ≤5 X ULN for participants with liver metastases
Albumin[c]	≥3.0 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks and G-SCF and thrombopoietin within last 3 weeks.

[b] Estimated creatinine clearance using Cockcroft-Gault:

$$\frac{(140\text{-age [years]} \times \text{weight [kg]})}{\text{Serum creatinine (mg/dL)} \times 72} \quad (\times F)^*$$

*where F = 0.85 for females and F = 1 for males

[c] Criteria must be met without albumin supplementation within the last 72 hours.

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

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has had previous therapy for locally advanced unresectable or metastatic gastric/GEJ/esophageal adenocarcinoma.

   Note: Participants may have received prior neoadjuvant or adjuvant therapy as long as it was completed at least 6 months prior to randomization and progression occurred at least 6 months after completion of therapy.

2. Has had major surgery within 28 days prior to first dose of study interventions.

   Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility

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

3. Has had radiotherapy within 14 days of randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

4. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

5. Has known CNS metastases and/or carcinomatous meningitis.

6. Has severe hypersensitivity (≥Grade 3) to treatment with an mAb or known sensitivity or intolerance to any component of lenvatinib, pembrolizumab, study chemotherapy agents and/or to any excipients, murine proteins, or platinum-containing products.

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

8. Has perforation risks or significant GI bleeding, such as:

   - Has had a serious nonhealing wound, peptic ulcer, or bone fracture within 28 days prior to randomization.

   - Has preexisting ≥Grade 3 GI or non-GI fistula.

- Has significant bleeding disorders, vasculitis, or has had a significant bleeding episode from the GI tract within 12 weeks prior to randomization.

9. Has GI obstruction, poor oral intake (CAPOX participants), or difficulty in taking oral medication (CAPOX participants). G-tubes, J-tubes and nasogastric tubes will not be permitted for treatment administration of capecitabine. Participants with existing esophageal stent are not eligible. Also, participants with known gastrointestinal malabsorption, gastrointestinal anastomosis or any other condition that may affect the absorption of lenvatinib.

Prior/Concomitant Therapy

10. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory TCR (eg, CTLA-4, OX40, CD137).

11. Has received prior therapy with anti-VEGF TKI or anti-VEGF mAb.

12. Has received a live or live-attenuated vaccine within 30 days before the first dose of study drug. Note: Killed vaccines are allowed.

    Note: See Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

14. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.
15. Has radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation.
    Note: The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy
16. Has inadequate cardiac function assessed as:

- LVEF below the institutional normal range as determined by a MUGA or ECHO.

- QTcF value >470 msec for males and >480 msec for females (mean of 3 measurements corrected for heart rate using Fridericia's formula).

Cardiac function will be assessed using 12-lead ECG scan and ECHO performed by the investigator or other qualified person prior to enrollment in the study. For country specific requirements, see Appendix 7.

17. Has urine protein ≥1 g/24 hours.
    Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants may be eligible if 24 hour urine protein ≤1 g.
18. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention.
19. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
20. Has a known history of active TB (Mycobacterium tuberculosis). No testing for TB is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
21. Has an active infection requiring systemic therapy.
22. Has poorly controlled diarrhea (eg, watery stool, uncontrollable bowel movement with supportive medication, Grade ≥2 and number of defecations, ≥5/day).
23. Has accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment. If the participant is receiving diuretic drugs for other reasons, it is acceptable. Consult with the Sponsor if the participant has more than trivial/trace fluid accumulation.
24. Has a history or current evidence of any condition (eg, but not limited to, known deficiency of the enzyme DPD, etc.), 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 investigator (refer to Appendix 7 for country-specific requirements). Participants with a contraindication to SOC therapy should be excluded based on the following:

    - Has a history of a GI condition or procedure that in the opinion of the investigator may affect oral study drug absorption.
    - Has a history of a severe and unexpected reaction to a fluoropyrimidine-containing treatment.
    - Has severe dyspnea at rest related to advanced disease stage or oxygen-dependent complications.

- Has hypokalemia, hypomagnesemia, or hypocalcemia.
- Participant had active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks or tumor bleeding within 2 weeks prior to the first dose of study intervention.

25. Has peripheral neuropathy ≥Grade 2.

26. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.

27. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. Note: Medically controlled arrhythmia would be permitted.

28. Has a known history of HIV (HIV antibodies). No testing for HIV is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

29. Has a known history of hepatitis B (defined as HBsAg reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. No testing for hepatitis B/C is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

Other Exclusions

30. Has weight loss of >20% within the last 3 months.

Country-specific requirements are listed in Appendix 7.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Photosensitivity

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

5.3.3 Caffeine, Alcohol, and Tobacco Restrictions

There are no restrictions in caffeine, alcohol and tobacco consumption/use.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

In Part 1, if one of the Safety Run-in participants does not receive at least 1 dose of lenvatinib plus pembrolizumab plus chemotherapy (either mFOLFOX6 or CAPOX), the participant will be replaced.

In Part 2, a participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

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

Global clinical supply complaints and/or temperature excursions are to be reported as soon as possible upon first becoming aware of the issue by completing the Online Form at www.csincident.msd.com or via email to clinical.complaints.intake@MSD.com in case of system downtime or technical issues with the online form.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 4.

Country-specific requirements are noted in Appendix 7.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab	Drug	Solution	25 mg/mL	400 mg	IV Infusion	Q6W	Test Product	IMP	Central
Arm 1	Experimental	Lenvatinib	Drug	Capsule	10 mg/ 4 mg / 1mg	8 mg induction/ 20 mg consolidation	Oral	Once daily	Test Product	IMP	Central
Arm 1	Experimental	Capecitabine (CAPOX)	Drug	Tablet	150 mg tablet or 500 mg tablet	1000 mg/m^2	Oral	BID for 14 days Q3W for 4 cycles	Test Product	IMP	Local and Central
Arm 1	Experimental	Oxaliplatin (CAPOX)	Drug	Solution	100 mg/ 20 mL vial or 50 mg vial	130 mg/m^2	IV Infusion	Once Q3W for 4 cycles	Test Product	IMP	Local and Central
Arm 1	Experimental	Oxaliplatin (mFOLFOX)	Drug	Solution	100 mg/ 20 mL vial or 50 mg vial	85 mg/m^2	IV Infusion	Once Q2W for 6 cycles	Test Product	IMP	Local and Central
Arm 1	Experimental	5-FU (mFOLFOX)	Drug	Solution	500 mg/ 10 mL vial or 250 mg/ 10 mL vial	400 mg/m^2 (bolus) plus 2400 mg/m^2 (continuous)	IV Infusion	Q2W for 6 cycles	Test Product	IMP	Local and Central
Arm 1	Experimental	Leucovorin or Levoleucovorin (mFOLFOX)	Drug	Solution	100 mg vial or 300 mg vial	400 mg/m² (or 200 mg/m² for levoleucovorin)	IV Infusion	Q2W for 6 cycles	Test Product	IMP	Local and Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Active Comparator	Capecitabine (CAPOX)	Drug	Tablet	150 mg tablet or 500 mg tablet	1000 mg/m^2	Oral	bid for 14 days q3w	Comparator	IMP	Local and Central
Arm 2	Active Comparator	Oxaliplatin (CAPOX)	Drug	Solution	100 mg/ 20 mL vial or 50 mg vial	130 mg/m^2	IV Infusion	q3w	Comparator	IMP	Local and Central
Arm 2	Active Comparator	Oxaliplatin (mFOLFOX)	Drug	Solution	100 mg/ 20 mL vial or 50 mg vial	85 mg/m^2	IV Infusion	q2w	Comparator	IMP	Local and Central
Arm 2	Active Comparator	5-FU (mFOLFOX)	Drug	Solution	500 mg/ 10 mL vial or 250 mg/ 10 mL vial	400 mg/m^2 (bolus) plus 2400 mg/m^2 (continuous)	IV Infusion	q2w	Comparator	IMP	Local and Central
Arm 2	Active Comparator	Leucovorin or Levoleucovorin (mFOLFOX)	Drug	Solution	100 mg vial or 300 mg vial	400 mg/m² (or 200 mg/m² for levoleucovorin)	IV Infusion	q2w	Comparator	IMP	Local and Central

AxMP=auxiliary medical product; bid=twice a day; IMP=investigational medicinal product; IV=intravenous.; NIMP=noninvestigational medical product,; q2w=every two weeks; q3w=every three weeks.; 5-FU= fluorouracil

The classification of IMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Investigator decision regarding the type of backbone chemotherapy (CAPOX or mFOLFOX6) should be determined prior to allocation/randomization. Participants should continue on the type of backbone chemotherapy chosen prior to randomization throughout the study.

Lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension (please refer to Pharmacy Manual).

Clinical supply concentration and formulation of chemotherapy may vary by local source.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 4 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements as per the "Sourcing" column.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of lenvatinib and pembrolizumab are provided in the Pharmacy Manual. For participants who have difficulty swallowing capsules, lenvatinib can be dissolved into a suspension. Please refer to Pharmacy Manual for full details. Concomitant chemotherapeutic agents will be prepared and administered as per the approved product labels.

The body surface area in m^2 should be calculated per local guidance. The dose of chemotherapy should be recalculated for fluctuation of body weight ≥10% at the beginning of a cycle only. For weight fluctuation <10%, recalculation may be performed at the discretion of the investigator. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard

and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

The Safety Run-in (Part 1), comprising approximately 12 participants, will be open-label and non-randomized. The Main Study (Part 2) will be open-label and randomized. Intervention allocation/randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to lenvatinib plus pembrolizumab plus chemotherapy study intervention and chemotherapy study intervention, respectively.

6.3.2 Stratification

Part 1 (Safety Run-in):

There are no stratification factors for Part 1.

6.3.3 Blinding

This is an open-label study (Part 1 and Part 2); therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified pembrolizumab treatment for ≥12 weeks, or lenvatinib treatment for ≥4 weeks, or chemotherapy treatment for ≥3 weeks require

consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Listed below are concomitant therapies prohibited during the course of the study:
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than lenvatinib or pembrolizumab
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion may be allowed at the investigator’s discretion.

- Live or live-attenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Administration of killed vaccines is allowed.

  Note: Any licensed COVID 19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  - Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed
- Systemic glucocorticoids are permitted only for the following purposes:

  - To modulate symptoms from an AE that is suspected to have an immunologic etiology.

    Note: Inhaled or topical steroids are allowed, and systemic steroids at doses ≤10 mg/day prednisone or equivalent are allowed.

  - The use of doses higher than 10 mg/day prednisone or equivalent may be approved after consultation with the Sponsor.
  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent).

  - A short course of steroids may be used as concomitant medication for either treatment of an AE or medical condition with Sponsor approval.

  - Use of prophylactic corticosteroids to avoid allergic reactions (eg, IV contrast dye or transfusions) is permitted.

  - The use of intermittent inhaled steroids or intranasal or local injection of corticosteroids is permitted.
  - Use of steroids for antiemetic purposes is permitted.

  - Use of steroids for premedication for chemotherapy, per local guidance may be permitted with Sponsor approval.

- For participants receiving 5-FU, or capecitabine:

  - Brivudine, Sorivudine analogs, and other inhibitors of the enzyme dihydropyrimidine dehydrogenase

Concomitant Medications to be Used with Caution

- Caution is advised when oxaliplatin and lenvatinib treatment is coadministered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored. Cimetidine, metronidazole and interferons may increase levels of 5-FU. Reliable sources such as crediblemeds.org can be used to assist in identification of medicinal products known to cause QT interval prolongation.
- 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 (increase in alkaline phosphatase, transaminase, or bilirubin levels) are frequently observed under the treatment with 5-FU and levamisole.
- For participants receiving oxaliplatin:
    - Caution is advised if medicinal products associated with rhabdomyolysis are administered concomitantly with oxaliplatin.

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

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. If participants experience an SAE or ECI, All concomitant medications administered during SAEs or ECIs (30 days or more after the last dose of study intervention) are to be recorded. SAEs and ECIs are defined in Section 8.4.

6.5.1 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. For participants receiving lenvatinib plus pembrolizumab, suggested supportive care measures for the management of AEs with potential immunologic etiology along with the dose modification guidelines are outlined in Section 6.6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or lenvatinib. Refer to Section 6.6.2 for guidelines regarding dose modification and supportive care.

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

6.5.1.1 Supportive Care Guidelines for Capecitabine

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

6.5.1.2 Supportive Care Guidelines for Oxaliplatin

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

6.5.1.3 Supportive Care Guidelines for 5-FU

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

6.5.2 Drug Interactions

There are no DDI-related concomitant medication prohibitions or restrictions.

Lenvatinib is not expected to clinically meaningfully alter exposure to CYP3A4/ Pgp substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and Pgp substrate).

Clinical studies also showed that coadministration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp are not of clinical concern.

No drug interaction is expected between lenvatinib and pembrolizumab because of their divergent metabolic pathways. Pembrolizumab is a mAb and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and nonenzymatic processes (lenvatinib IB).

6.5.3 Concomitant Surgery

In general, surgical resection in participants who have metastatic disease is not encouraged except in exceptional cases as the benefit of surgery is unknown in this setting. However, if it is determined that participants are eligible for potential curative surgical resection, in the event of strong tumor response, please contact the Sponsor for guidance. Participants who have curative surgery while on study will be defined as are participants who have had tumor resection and a postresection imaging restaging to include at minimum contrasted CT chest, abdomen, pelvis, plus imaging of any part of the body previously known to have tumor and must show no residual disease. MRI with IV contrast or PET CT may be allowed if appropriate for restaging imaging. Participants who have surgery should continue imaging as detailed in the SoA (Section 1.3) until PD, or they otherwise meet the discontinuation criteria (Section 7.1).

6.6 Dose Modification (Escalation/Titration/Other)

Adverse events will be graded using NCI CTCAE v5.0. Investigators will decide the probability of the event being related to one or more drugs as to whether dose modification of one or more drugs is required.

This is an open-label protocol with a novel combination of pembrolizumab, lenvatinib, and chemotherapy (CAPOX or mFOLFOX6). Because of the multiple agents included in this protocol, overlapping toxicities may occur and the determination of the contribution of agents to specific toxicities may be challenging. Dose modifications can be handled individually or in concert depending on determined relatedness. Refer to Section 6.6.2, Section 6.6.3 and Section 6.6.4 for guidance with regards to dose interruption, dose modification, and overlapping toxicities. Please contact the Sponsor for additional guidance if needed.

Participants who interrupt or discontinue one of the study medications (pembrolizumab, lenvatinib, or chemotherapy) due to toxicity may continue with the other drug(s) in the combination until the criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression).

6.6.1 Initial Treatment or First Course

The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 18 doses may be eligible for retreatment if they progress after stopping study intervention provided, they meet the requirements detailed in Section 6.6.6. Participants may be retreated in Second Course (Retreatment) for up to an additional 9 cycles (approximately 1 year).

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

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.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

Table 5 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 (CTCAE v5.0)	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 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 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 [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	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		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	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 based on the event [e]		
	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] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] 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.

[e] Events that require discontinuation include, but are not limited to: encephalitis 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 reaction are provided in Table 6.

Table 6 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 intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruptions 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 6 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.3 Lenvatinib Dose Modification and Toxicity Management

Lenvatinib dose modification during Safety Run-in (Part 1), induction, dose guidance to start consolidation, and dose modification during consolidation are specified below. Variation in dose modification guidance is because of differences in treatment regimen and recommended starting dose. Please refer to the section that applies to the correct phase of therapy (ie, induction or consolidation).

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CCI

[redacted]

CCI

[redacted]

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[redacted]

CCI

[redacted]

6.6.3.3 Management of QT Prolongation

Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium and replenish as appropriate.

6.6.3.4 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 1.3). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications). Refer to Appendix 8 (Figure 8, Figure 9) for additional information on the management of hypertension during Induction and Consolidation.

If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the participant's clinical circumstances and follow standard medical practice. For previously normotensive participants, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a participant is at imminent risk to develop a hypertensive crisis or has uncontrolled hypertension with significant risk factors for severe complications (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the participant has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment

cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on 2 BP assessments at least 30 minutes apart:

1. Continue study drug and institute antihypertensive therapy for participants not already receiving this.
2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.
3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

    - Additional dose reduction should be discussed with the Sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

1. Institute appropriate medical management

2. Discontinue study intervention

6.6.3.5 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA (Section 1.3). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the SoA (Section 1.3). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipstick is not feasible.

2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot UPCR test) is required in the following situations:

    - The first (initial) occurrence of ≥2+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while the participant is receiving lenvatinib.
    - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level.

        - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL). A 24-hour urine collection (initiated as soon as possible and at least within 24 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained. If the participant has a 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 8.

Monitoring

- Urine dipstick testing or urinalysis for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed Q2W (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 6 weeks.
- Proteinuria monitoring can be performed at the local laboratory or investigator site but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.
- If proteinuria does not resolve, a nephrology consultation is recommended.

6.6.3.6 Management of Diarrhea

An antidiarrheal agent should be recommended to the participant at the start of study treatment and participants should be instructed and educated to initiate antidiarrheal treatment at the first onset of soft bowel movements. The choice of antidiarrheal agent should

be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 8 should be followed.

6.6.3.7 Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the SoA (Section 1.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 8 and Table 9 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per NCI CTCAE v5.0) occurs, lenvatinib must be discontinued. Hepatic failure is defined as per the CTCAE definition.

6.6.3.8 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis signs including lower extremity swelling, and warmth to touch or tenderness. If any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 8 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, lenvatinib must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require lenvatinib discontinuation.

6.6.3.9 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 8 should be followed.

6.6.3.10 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3). Corrected serum calcium should be used to assess the grade of hypocalcemia per NCI CTCAE v5.0, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] × 0.8 + serum calcium)

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and vitamin D supplementation) until resolution.

6.6.3.11 Management of Hemorrhage

Guidelines in Table 8 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.6.3.12 Management of Gastrointestinal Perforation or Fistula Formation

Participants with gastric cancer are at increased risk for GI perforation and fistula formation. Lenvatinib should be discontinued in any participants who develop GI perforation of any grade or Grade 4 fistula.

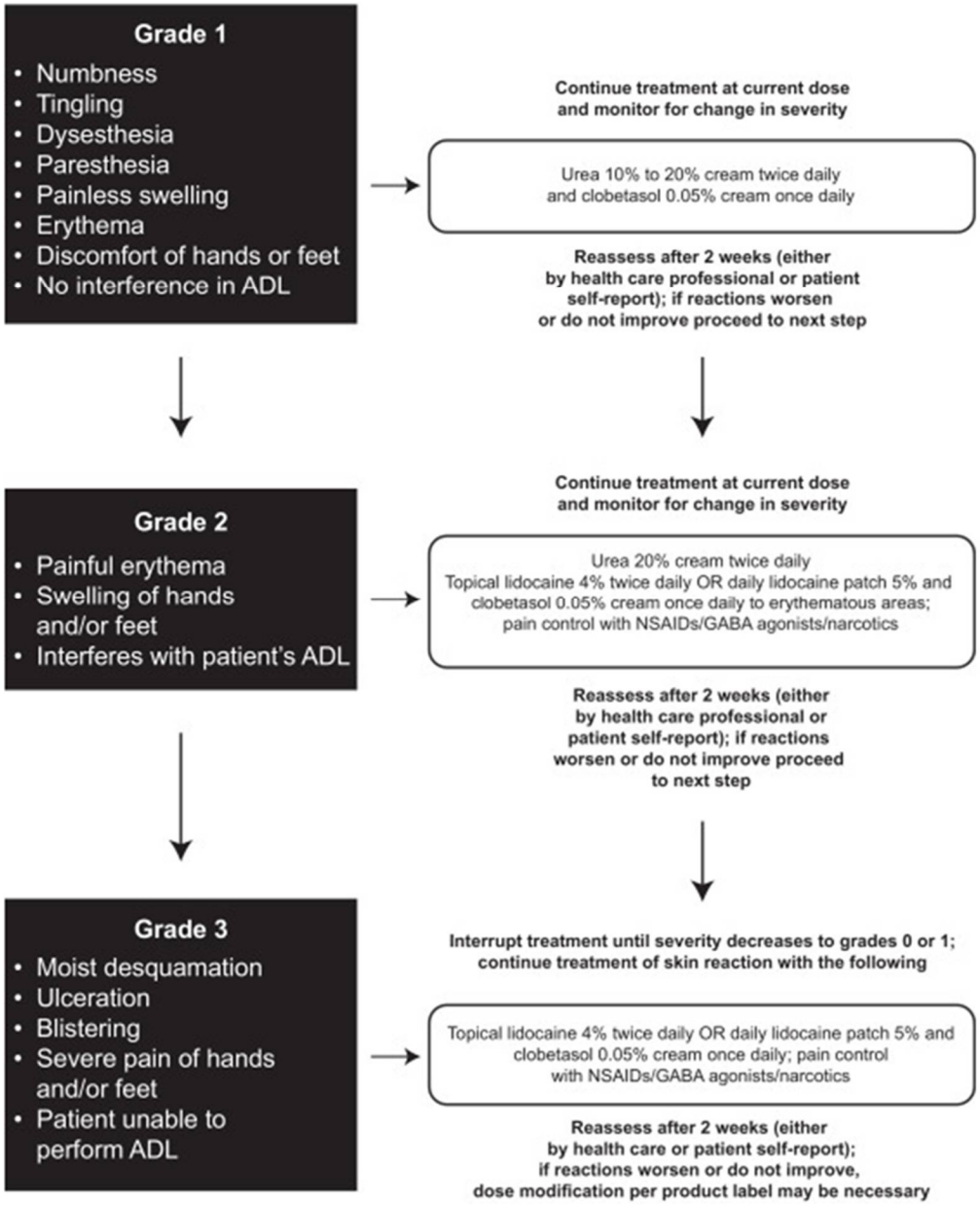
6.6.3.13 Management of Palmar-plantar Erythrodysesthesia Syndrome

PPES is common across TKI therapies, and the strategies used for managing PPES in participants receiving TKIs (lenvatinib) range from preventative measures to topical medication once it has developed [Lacouture, M. E., et al 2014] [Lacouture, M. E., et al 2008].

Participants should be educated about the visible signs of PPES to help with the early detection of symptoms [Lacouture, M. E., et al 2014]. During treatment, participants should be encouraged to reduce exposure of the hands and feet to hot water, avoid tight footwear, and limit damage caused by vigorous exercise. Prophylaxis may include pretreatment examination of the soles of the feet and palms and removal of any existing hyperkeratotic areas and calluses present, which can then be protected by cushioning and treated with moisturizing creams and keratolytic agents [Lacouture, M. E., et al 2008]. A suggested treatment algorithm for PPES is outlined in Figure 5.

As most participants develop PPES within the first 2 to 4 weeks of initiating TKI therapy, avoiding traumatic activity and having sufficient rest during this time may be important [Lacouture, M. E., et al 2008]. PPES management can require dose reduction or interruption of lenvatinib treatment until the AE has resolved back to ≤Grade 1 severity [Lacouture, M. E., et al 2008]. It may also be appropriate to consult with a dermatologist and/or podiatrist for participants experiencing persistent Grade 2 or Grade 3 PPES.

Figure 5 Treatment Algorithm for Palmar-Plantar Erythrodysesthesia



ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse Events; GABA=gamma-aminobutyric acid; NSAIDs=nonsteroidal anti-inflammatory drugs.
Source: [Lacouture, M. E., et al 2014] [Lacouture, M. E., et al 2008]

6.6.3.14 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold

lenvatinib if ONJ develops and restart based on clinical judgment of adequate resolution (see Section 6.6.3.15).

6.6.3.15 Other Allowed Dose Interruptions for Lenvatinib

If the participant is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.
- For participants who experience hand-foot syndrome that is related to both capecitabine and lenvatinib dosing, it is recommended that the capecitabine dose be reduced first, as described in Table 10.

6.6.4 Dose Modifications for Overlapping Toxicities

In this study, participants will be administered multiagent/multitargeted anticancer therapy. Although ample safety data are available for each of the components of recommended treatment regimens, the combination of all treatment medications is expected to have potential overlapping toxicities. As this study is open-label, participant safety will be actively monitored, as well as reviewed by an eDMC. A 21-day Safety Run-in including approximately 12 participants will evaluate safety as detailed in Section 4.1. Potential expected overlapping toxicities for participants on this study may include, but not limited to, hematologic, GI toxicity, cardiac toxicity, skin toxicity, and renal toxicity.

6.6.4.1 Lenvatinib and Pembrolizumab

Based on the known toxicity profiles of lenvatinib and pembrolizumab, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while irAEs are risks for pembrolizumab treatment. However, certain AEs, such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

    - Because lenvatinib dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q6W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:
        - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.

- If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

If the participant recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

   If an AE is suspected to be treatment-related and is severe/life-threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, Type 1 diabetes mellitus) and other supportive care should be taken promptly.

3. Participants receiving combination therapy (lenvatinib + pembrolizumab) must discontinue study intervention if any of the following occur:

   a. ALT or AST >5 X ULN for more than 2 weeks. Pembrolizumab will have already been permanently discontinued per Table 5, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
   b. ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5). Although Table 5 advises pembrolizumab to be withheld (interrupted), Table 8 and Table 9 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

6.6.4.2 Chemotherapy

The investigator may also attribute each toxicity event to the chemotherapy administered (capecitabine, oxaliplatin, and/or 5 FU). Dose modification should be performed taking the following criteria into consideration.

- Treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to the guideline for restarting each study treatment.

- If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated.

- Dose reduction of only one chemotherapy agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to a combination of 2 chemotherapy agents, the dose of both drugs may be reduced according to the recommended dose modifications. If the toxicity is considered related to the combination of 3 agents, chemotherapy may be considered to be reduced, interrupted or discontinued. Lenvatinib and/or pembrolizumab should be interrupted or discontinued according to the recommended dose modifications (Section 6.6.2 and Section 6.6.3, respectively).

- If any adjustments to the chemotherapy dose modification guidelines are required per local guidelines, a Sponsor consultation is strongly recommended.

If toxicity is not otherwise specified, investigators should refer to the label or local guidelines for oxaliplatin, 5-FU, and capecitabine for dose adjustments.

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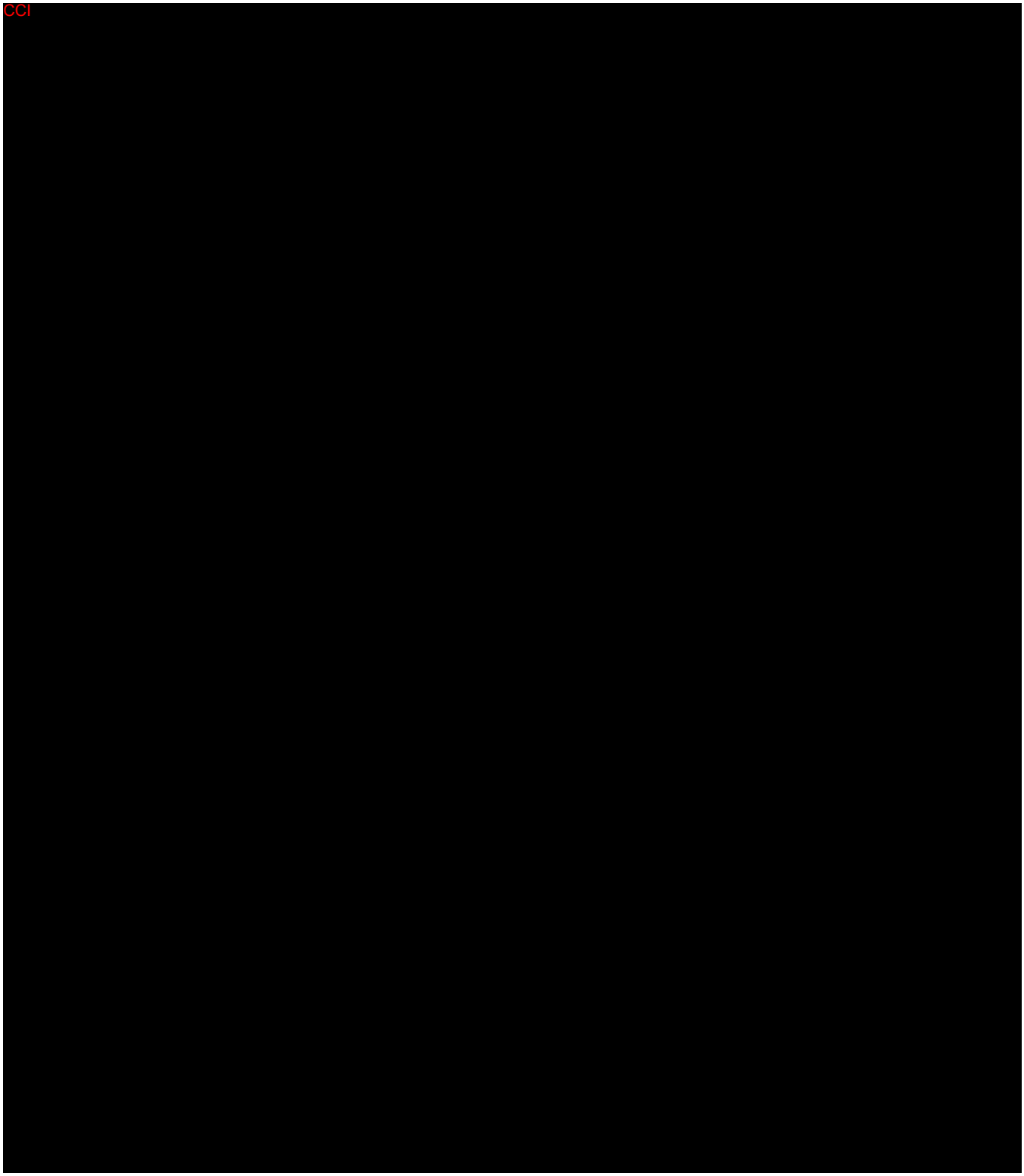

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6.6.5 Chemotherapy Dose Modification

Dose delays and treatment restarts will be made at the discretion of the site investigator according to institutional guidelines or local standard practice. If any adjustments to the chemotherapy dose modification guidelines are required per local guidelines, a Sponsor consultation is strongly recommended. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated.

In participants with unrecognized DPD deficiency, acute, life-threatening toxicity may occur when participants are treated with fluoropyrimidine. We recommend DPD testing as appropriate per local guidelines. Participants who require dose modification on Cycle 1 are not eligible for the study.

6.6.5.1 CAPOX (Capecitabine/Oxaliplatin)

CAPOX treatment will comprise the following:

- Capecitabine (1000 mg/m^2, bid for 14 days, Q3W)
- Oxaliplatin (130 mg/m^2, IV infusion, Q3W)

For capecitabine, older participants are more susceptible to the effects of fluoropyrimidine-based therapies with increased Grade 3/4 adverse effects, especially when used in combination. For oxaliplatin, participants ≥ 65 years have a higher incidence of GI toxicity, myelosuppression, syncope and fatigue. No dose adjustments are needed but caution should be exercised.

Dose modifications for CAPOX are outlined in Table 10 and Table 11.

Table 10 Recommended Dose Modification (Reduction) Guidelines for CAPOX Drug-Related Adverse Events

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

BID=twice daily

Table 11 Recommended Dose Modification Guidelines for CAPOX Drug-Related Adverse Events

Category	Toxicity		Oxaliplatin	Capecitabine
Hematologic	Neutropenia[a]	3[b]	Hold until neutrophil count resolves to ≥1500/mm^3 No reduction (*consider G-CSF)	Hold until neutrophil count resolves to >1500/mm^3 No dose reduction (consider G-CSF)
		4[b]	Hold until neutrophil count resolves to ≥1500/mm^3 Reduce by 1 DL (*recommend G-CSF)	Hold until neutrophil count resolves to >1500/mm^3 Reduce by 1 DL (consider G-CSF)
	Febrile neutropenia[a]	3[b]	Hold until neutrophil count resolves to ≥1,500/mm^3 • First occurrence: Consider G-CSF • Second occurrence: Dose reduce by 1 DL *recommend G-CSF • Further occurrences: Dose reduce by 2 DL *recommend G-CSF	Hold until toxicity resolves to Grade 0-1 Reduce by 1 DL
		4[b]	Discontinue	Discontinue
	Thrombocytopenia	1-2	Hold until platelet count resolves to >75,000/mm^3. For first occurrence, no change in dose. For further occurrence dose reduce by 1 DL each occurrence.	Hold until platelet count resolves to >75,000/mm^3. First occurrence no change in capecitabine dose. For further occurrences dose reduce by 1 DL for each occurrence.
		3-4[b]	Hold until platelet count resolves to >75,000/mm^3 Reduce by 1 DL	Hold until platelet count resolves to >75,000/mm^3. Reduce by 1 DL

Category	Toxicity		Oxaliplatin	Capecitabine
Neurotoxicity	Persistent paresthesia		Reduce 1DL	No holding dose. No change in dose
	Persistent Paresthesia with pain		Reduce 2DL or discontinue	No holding dose. No change in dose
	Paresthesia with functional impairment		Reduce 2DL if lasting 7-14 days or discontinue if persistent	No holding dose. No change in dose
Hepatic impairment	Bilirubin 1 to 2 x ULN		No change	Caution
	Bilirubin >2 to 4 x ULN **AND/OR** AST/ALT 2 to 4 x ULN		No change	Caution
	Bilirubin >4 x ULN **AND/OR** AST/ALT 4 x ULN		No data available	OMIT if bilirubin >4 x ULN
	Bilirubin ANY **OR** AST/ALT >4 x ULN		No data available	OMIT if bilirubin >4 x ULN)
Renal impairment	Creatinine clearance: 50 to 80 mL/min		No change	No dose reduction with close monitoring
	Creatinine clearance: 30 to <50 mL/min		Caution, consider dose reduction	Reduce by 1 DL (use with caution)
	Creatinine clearance: <30 mL/min		Discontinue	Discontinue
Other	Diarrhea, mucositis, or hand-foot syndrome	2-3	Strongly consider discontinuing for diarrhea associated with severe infectious colitis/typhlitis. Reduce by 1DL (or consider discontinue) for diarrhea associated with febrile neutropenia or sepsis.	Hold until toxicity resolves to Grade 0-1 Reduce by 1 DL
		4	Hold until resolves to Grade 1 or 2 Reduce by I DL	Discontinue
	Other toxicities[c]	3-4[b]	First occurrence: Reduce by 1 DL Second occurrence: Reduce by 2 DL	Hold until toxicity resolves to Grade 0-1 Reduce by 1 DL
	Laboratory adverse events	3-4[b]	Hold until toxicity resolves to Grade 0-1 Reduce by 1 DL	Hold until toxicity resolves to Grade 0-1 Reduce by 1 DL

Category	Toxicity	Oxaliplatin	Capecitabine
DL=dose level; 5-FU=5-fluorouracil; G-CSF=granulocyte colony-stimulating factor; N/A=not applicable. [a] May consider restarting when neutrophil count resolves to ≥1000/mm^3 per local guidance. [b] Permanent discontinuation should be considered for any severe or life-threatening event and/or if toxicity does not resolve within 4-5 weeks of last administration. [c] 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. *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 NCI-CTC Grade 4 neutropenia or; delay of one therapy cycle because of leukopenia or neutropenia by more than 3 days.			

6.6.5.2 mFOLFOX6

mFOLFOX6 treatment will comprise the following:

- Oxaliplatin (85 mg/m^2, IV infusion, Q2W)
- 5-FU (400 mg/m^2, bolus IV infusion followed by 2400 mg/m^2 continuous IV infusion, Q2W)
- Leucovorin (400 mg/m^2, IV infusion, Q2W) or levoleucovorin (200 mg/m^2, IV infusion, Q2W)

Refer to Table 12 for dose modification criteria for mFOLFOX6.

Table 12 Recommended Dose Modification Guidelines for mFOLFOX6 Drug-related Adverse Events

Category	Toxicity Grade		Oxaliplatin[a]	5-FU
Hematological	Neutropenia[a]	3-4	Hold until neutrophil count resolves to ≥1,500/mm^3 Reduction from 85 mg/m^2 to 75 mg/m^2	Hold until neutrophil count resolves to >1500/mm^3 Reduce by 20% (consider G-CSF)
	Febrile neutropenia[a]	3-4	Hold until neutrophil count resolves to ≥1,500/mm^3 Reduction from 85 mg/m^2 to 75 mg/m^2	Hold until neutrophil count resolves to >1500mm^3 Reduce by 20% (consider G-CSF)
	Thrombocytopenia[b]	3-4	Hold until platelet count resolves to > 75 000/mm^3. Reduction from 85 mg/m^2 to 75 mg/m^2	Hold until platelet count resolves to >75 000/mm^3. Reduce by 20%

Category	Toxicity Grade	Oxaliplatin[a]	5-FU
Neurotoxicity	Persistent[c] Grade 1 or 2 neurotoxicity	Reduction from 85 mg/m^2 to 75 mg/m^2	No change
	Transient[c] Grade 3 neurotoxicity	Reduction from 85 mg/m^2 to 75 mg/m^2	No change
	Persistent[c] ≥ Grade 3 neurotoxicity **OR** any Grade 4 neurotoxicity	Discontinue	No change
	PRES/RPLS	Discontinue permanently	
Hepatic Impairment	Bilirubin 1 to 2 x ULN	No change	Caution
	Bilirubin >2 to 4 x ULN **AND/OR** AST/ALT 2.5 to 5 x ULN	No change	Caution
	Bilirubin >4 x ULN **AND/OR** AST/ALT 5 x ULN	No data available	OMIT if bilirubin >4 x ULN (Leucovorin to be omitted if 5-FU omitted)
	Bilirubin ANY **OR** AST/ALT >5 x ULN	No data available	OMIT if bilirubin >4 x ULN (Leucovorin to be omitted if 5-FU omitted)
Renal Impairment	Creatinine clearance: 50 to 80 mL/min	No change	No change
	Creatinine clearance: 30 to <50 mL/min	Caution, consider dose reduction	No change; monitor
	Creatinine clearance: <30 mL/min	Discontinue	Consider dose reduction
Other	≥ Grade 3 GI toxicity (after prophylaxis)	Hold until resolves to Grade 0-1 Reduction from 85 mg/m^2 to 75 mg/m^2 [c]	Hold until resolves to Grade 0-1 Reduce by 20%[c]
	Sepsis/septic shock	Discontinue	Discontinue
	Hemolytic uremic syndrome **OR** any signs of microangiopathic hemolytic anemia	Discontinue permanently	
	Other ≥ Grade 3 related organ toxicity[d]	Reduction from 85 mg/m^2 to 75 mg/m^2	Reduce by 20%

Category	Toxicity Grade	Oxaliplatin[a]	5-FU
5-FU=fluorouracil; ALT=alanine aminotransferase; AST=aspartate aminotransferase; RPLS=reversible posterior leukoencephalopathy syndrome; ULN=upper limit of normal Further dose reduction may be considered on Sponsor's approval. Do not retreat until the ANC ≥1.5 x 10^9/L and the platelets ≥75-100 x 10^9/L, GI and neurotoxicities have resolved and other nonhematologic toxicities ≤ Grade 1. a May consider restarting when neutrophil count resolves to ≥1000/mm^3 per local guidance. b Discontinue if sepsis/septic shock. c Transient ≥7days-<1 cycle; persistent ≥1 cycle. d For skin toxicity, reduce 5-FU dose only.			

For participants in the lenvatinib plus pembrolizumab plus chemotherapy arm: if chemotherapy (CAPOX/mFOLFOX6) is interrupted due to adverse events, the participants may extend the Induction Phase for a maximum of 6 weeks on approval by the Sponsor. The participant should not exceed 4 cycles of CAPOX treatment, or 6 cycles of mFOLFOX6 treatment.

6.6.6 Second Course

Note: As of Amendment 8, Second Course will no longer be offered. Any participant currently receiving Second Course retreatment will be able to continue treatment as planned. Imaging will be performed per local standard of care. Participants who either complete 18 cycles of pembrolizumab or discontinue pembrolizumab will be discontinued from the study following the Safety Follow-up visit. AE, SAE, and other reportable safety events will be reported and followed as described under Section 8.4. All participants in Efficacy Follow-up prior to initiation of Amendment 8 will stop efficacy assessments and be discontinued from the study. All participants in Survival Follow-up are considered to have completed the study and should have a final survival contact; these participants will no longer be contacted for survival information.

Participants who stop study intervention with SD or better and have radiographic disease progression verified by a BICR, may be eligible for up to an additional 9 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping study intervention from the initial treatment phase.

This retreatment is termed the Second Course. Participants must provide new documented informed consent using the most recent IRB-approved version of the main consent form prior to starting the Second Course. All participants who receive the Second Course must be given pembrolizumab. In addition, participants who did not discontinue lenvatinib in the First Course (due to lenvatinib-related AEs) may begin the Second Course with lenvatinib at the highest tolerable dose received during the Consolidation Phase, per investigator's decision.

The Second Course phase of this study is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial study intervention after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
- Was treated with at least 4 cycles of pembrolizumab before discontinuing treatment, and
- Received at least 1 treatment with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study intervention after completion of 18 administrations (approximately 2 years) of study intervention for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
- On unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
- No new anticancer treatment was administered after the last dose of study intervention, and
- The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
- The study is ongoing.

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

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.11.3.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen at any time during the course of the study.
- Confirmed radiographic disease progression outlined in Section 8.2.1.5. In some rare circumstances, the investigator may believe the participant could benefit from continuing on study treatment. In these cases, the participant must continue to show clinical stability as defined in Section 8.2.1.5, and the Sponsor should be consulted for approval.

Considerations for evaluation of whether a participant may continue treatment after confirmed disease progression include:

- Presence or absence of clinical symptoms or signs indicating clinically significant disease progression

- Decline in performance status
- Lack of rapid disease progression or threat to vital organs or critical anatomic sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention
- Presence or absence of significant, unacceptable or irreversible toxicities related to study treatment
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment

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

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

Information regarding the amount of blood collected from each participant over the duration of the study can be found in the Laboratory Manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 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 study protocol number, study

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 ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or 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.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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.

Prior to entering Second Course, participant must provide documented informed consent using the most recent IRB-approved version of the main consent form.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

8.1.4.1 General Medical History

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

Medical history will include all active conditions, drug allergies, significant medical procedures, smoking status, and any condition diagnosed within the previous 10 years that is considered to be clinically important by the investigator. Any cancer, other than the cancer under study, will be recorded as medical history, even if diagnosed greater than 10 years before enrollment. Details regarding the cancer under study will be recorded separately and not listed as medical history.

8.1.4.2 Oncologic Disease Details

The investigator or qualified designee will obtain historic and current details of the participant's cancer under study. This information will include, but is not limited to, date of diagnosis, stage, histology, location(s) of primary lesions, and location(s) of metastases, if applicable.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before the first dose of study intervention.

8.1.5.2 Prior Oncologic Treatment

The investigator or qualified designee will review and record all treatments for the cancer under study, including systemic and local treatment, vaccinations, radiation, and surgeries. Additional information collected on these treatments will include, but is not limited to, reason for discontinuation, best response, and date of progression after each treatment as applicable.

8.1.5.3 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. Concomitant medications will be recorded for 30 days after the last dose of study intervention (or 90 days if used to treat an SAE). In addition, medications taken 30 days before the first dose of the Second Course Treatment, during the Second Course Treatment Phase, and for 30 days after the last dose of the Second Course Treatment (or 90 days if used to treat an SAE) will be recorded.

Any new anticancer therapy started after the participant's discontinuation from the treatment period will be recorded separately. Additional information collected on this treatment will include, but is not limited to, best response and date of progression.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before allocation/randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused 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/rescreening visit requirements are provided in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

In Part 2, 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 reassigned to another participant.

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. Administration of pembrolizumab, lenvatinib and CAPOX/mFOLFOX6 are detailed in Sections 8.1.8.1 and 8.1.8.2.

Study intervention should begin within 3 days of allocation.

8.1.8.1 Timing of Dose Administration

Study treatment in all arms will begin on Day 1 of each 6-week dosing cycle after all procedures/assessments have been completed as detailed in the SoA (Section 1.3). Study treatments may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All study treatments may be administered on an outpatient basis.

Treatments will be administered in the order presented below:

- Pembrolizumab infusion will be administered first, followed by lenvatinib, then oxaliplatin infusion, and then other treatment regimens will be administered.

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

receives 18 administrations (approximately 2 years) of study medication, achievement of a CR, or administrative reasons requiring cessation of treatment.

Note: Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (ie, elective surgery, unrelated medical events, participant vacation, and holidays) not related to study therapy. Participants should be placed back on study therapy as soon as clinically appropriate per the investigator, and not exceeding 6 weeks from the interrupted dosing. Day 1 of subsequent cycles should be adjusted accordingly to adhere to Q6W dosing schedule. Discuss with the Sponsor if participants cannot restart study medication within 6 weeks. The reason for interruption should be documented in the participant's study record.

8.1.8.1.1 Pembrolizumab

Pembrolizumab will be administered by IV infusion over 30 minutes as the first study intervention on Day 1 of each 42-day cycle. Sites should 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 0 minutes: -5/+10 minutes). After Cycle 1 Day 1, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle for administrative reasons.

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Concomitant chemotherapeutic/immunotherapeutic agents will be prepared and administered as per the approved product label(s).

8.1.8.1.2 Lenvatinib

Lenvatinib 8 mg (2 4 mg capsules) once daily will be taken orally with water (with or without food) at approximately the same time each day in each 42-day cycle. However, on Day 1 of each pembrolizumab cycle, lenvatinib will be administered in the clinic 0 to 4 hours after completion of pembrolizumab administration.

After the last cycle of the Induction Phase, lenvatinib will be maintained at the current dose (usually 8 mg daily if there are no dose reductions) until the start of the Consolidation Phase. The Consolidation Phase, and the corresponding lenvatinib dose escalation to 20 mg, will begin 3 weeks after the start of the last cycle of induction for CAPOX and 3 weeks after C2D29 of mFOLFOX6, when the dose will be escalated to 20 mg in participants who tolerated 8 mg. Refer to Section 6.6.3 for detailed guidance on dose modification and escalation.

8.1.8.1.3 CAPOX

Oxaliplatin 130 mg/m^2 IV infusion will be administered on Day 1 of Weeks 1 and 4 of each Q6W cycle.

Capecitabine 1000 mg/m^2 will be administered orally BID on Days 1-14, 22-35 of each Q6W cycle.

Note: Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (ie, elective surgery, unrelated medical events, participant vacation, and holidays) not related to study therapy. Participants should be placed back on study therapy as soon as clinically appropriate per the investigator, and not exceeding 3 weeks from the interrupted dosing. Day 1 of subsequent cycles should be adjusted accordingly to adhere to Q6W dosing schedule. Discuss with the Sponsor if participants cannot restart study medication within 3 weeks. The reason for interruption should be documented in the participant's study record.

In Arm 1, CAPOX will be administered for 4 x Q3W cycles during induction and will not be administered during consolidation.

In Arm 2, duration of oxaliplatin may be capped at 6 to 8 x Q3W cycles as per local country guidelines; however, treatment with capecitabine may continue per protocol.

8.1.8.1.4 mFOLFOX6

Oxaliplatin 85 mg/m^2 will be administered by IV infusion on Day 1 and Week 1, 3 and 5 of each Q6W cycle.

Leucovorin 400 mg/m^2 or levoleucovorin 200 mg/m^2 will be administered by IV infusion on Day 1, and Week 1, 3 and 5 of each Q6W cycle.

5-FU 400 mg/m^2 bolus IV infusion followed by 2400 mg/m^2 continuous IV infusion, will be administered on Day 1, and Week 1, 3, 5, of each Q2W cycle.

In Arm 1, mFOLFOX6 will be administered for 6 x Q2W cycles during induction and will not be administered during consolidation.

In Arm 2, the duration of mFOLFOX6 may be capped at 9 to12 x Q2W cycles per local country guidance.

8.1.8.2 Treatment Compliance

8.1.8.2.1 Lenvatinib

During onsite visits, lenvatinib will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. The administration, the dose, the time of administration, as well as any immediate reactions at the time of intake will be documented in the eCRF.

On all other days, lenvatinib will be taken at home. When a participant attends a study visit, he or she will bring any unused tablets.

Lenvatinib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance and investigators, and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

8.1.8.2.2 Pembrolizumab/CAPOX/mFOLFOX6

Pembrolizumab will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. CAPOX and mFOLFOX6 will be administered as per local guidelines. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the end of treatment visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

The process for scan collection and transmission to the iCRO can be found in the Site Imaging Manual. Tumor scans are strongly preferred to be acquired by CT. For the chest, abdomen and pelvis, contrast enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same scan technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on scans. Note: For the purposes

of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

Participant eligibility will be determined using investigator assessment. All scheduled scans for all participants from the sites will be submitted to the iCRO. In addition, scans (including via other modalities) that are obtained at an unscheduled time point to determine disease progression (regardless of whether disease progression was verified or not), as well as scans obtained for other reasons, but which demonstrates radiologic progression, should also be submitted to the iCRO.

When the investigator identifies disease progression, the iCRO will verify this progression and email the results to the study site and Sponsor (see Section 8.2.1.5 and Figure 6). In clinically stable participants, scans are to continue until disease progression has been verified by BICR. If initial investigator-assessed progression was not verified by BICR, each subsequent scan must be submitted to the iCRO. Once progression is verified by BICR, subsequent scans (if acquired) should not be submitted to the iCRO.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of randomization. Any scan obtained after Cycle 1 Day 1 of treatment cannot be included in the screening assessment. The site study team must review screening scans to confirm the participant has measurable disease per RECIST 1.1. The screening scans must be submitted to the iCRO for retrospective review.

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

8.2.1.2 Tumor Scans During the Study

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

Note: Imaging following approval of Amendment 8 is not required. For participants active on treatment, imaging should be performed per local standard of care. Scans performed per local standard of care are not required to be provided to the iCRO.

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

On-study bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and bone lesions existed at baseline).

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

If participants discontinue study treatment, tumor scans should be performed at the time of treatment discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan. Note: Following approval of Amendment 8, follow-up tumor scans are not required. Scans performed per local standard of care are not required to be provided to the iCRO.

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

8.2.1.4 Second Course (Retreatment) Tumor Scans

Note: Imaging following approval of Amendment 8 is not required. For participants active on treatment, imaging should be performed per local standard of care. Scans performed per local standard of care are not required to be provided to the iCRO.

If disease progression has been verified by BICR for the First Course, the Second Course may be initiated. The disease progression scan may also be used as the Second Course baseline scan if performed within 4 weeks prior to dosing and meets the scan standards.

The first scan should be performed within 28 days prior to restarting study intervention. Subsequent tumor scans are to be performed every 12 weeks (84 days ± 7 days) after the restart of study intervention or more frequently if clinically indicated.

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

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

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans every 12 weeks (±7 days) until the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

Response assessments and progressive disease are determined by investigator assessment.

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

Refer to Section 6.6.6 for further details on Second Course (Retreatment).

8.2.1.5 RECIST 1.1 Assessment of Disease

Note: Imaging following approval of Amendment 8 is not required. For participants active on treatment, imaging should be performed per local standard of care. Scans performed per local standard of care are not required to be provided to the iCRO.

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

On investigator-assessed disease progression, the indicative scans are to be submitted immediately to iCRO for BICR verification of progression. After submission of scans, the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
    - Resume imaging per protocol schedule (≥4 weeks to next scan)
    - Send scans to iCRO
    - Continue local assessment
    - Do not change investigator assessment of progression
    - If subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification
- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

If disease progression is verified, the process continues as follows:

1. Investigator judgment will determine action

2. If the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a documented reconsent addendum must be provided

    - Note: the documented reconsent addendum may be provided any time after investigator-assessed progression is identified but must be provided prior to starting study intervention after verification of disease progression is provided by the iCRO.

    - Obtain scans locally per original protocol schedule

    - Do not send scans to iCRO

Figure 6 illustrates the decision process involving verification of disease progression for participants.

For the purpose of this decision process, lack of clinical stability is defined as:

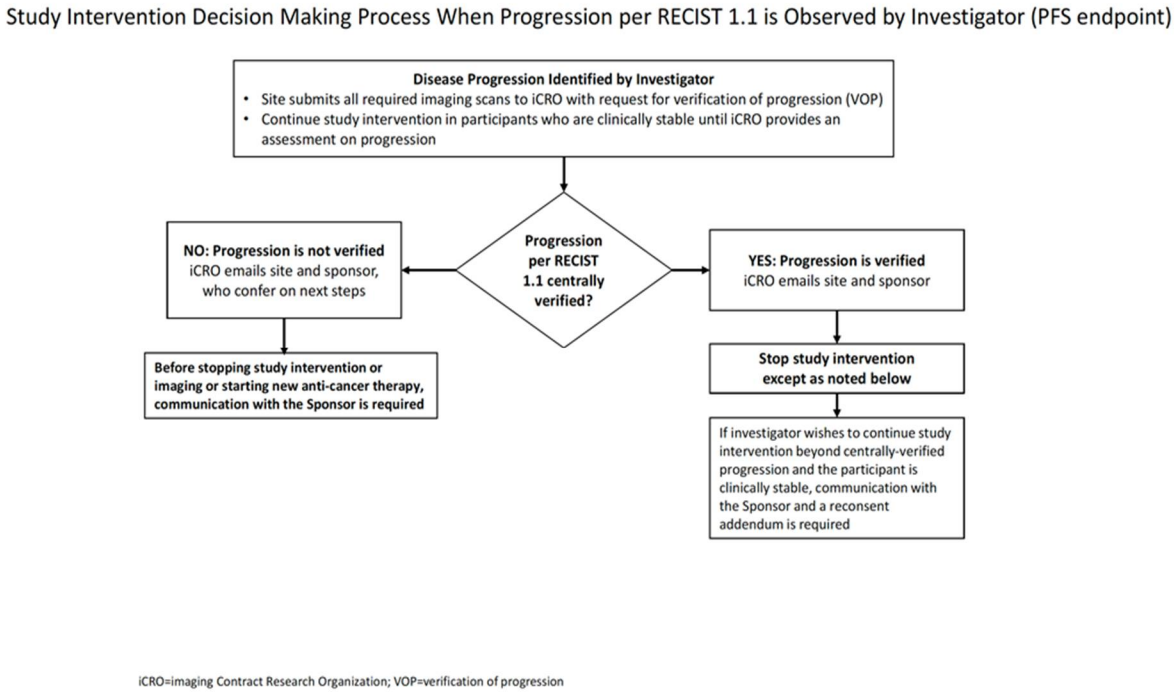
1. Unacceptable toxicity

2. Clinical signs or symptoms indicating clinically significant disease progression

3. Decline in performance status

4. Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

Figure 6 Decision-making Process When Progression Observed by Investigator



iCRO=imaging Contract Research Organization; VOP=verification of progression

CCI

[redacted]

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. Information on the amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), can be found in the Laboratory Manual.

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

8.3.1 Physical Examinations

A complete physical examination including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard during the Screening period and as indicated in the SoA (Section 1.3). Height and weight will also be measured and recorded. Clinically significant abnormal findings at Screening should be recorded as medical history. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

For cycles that do not require a full physical examination per the SoA (Section 1.3), the investigator or qualified designee will perform a directed physical examination including oral examination as clinically indicated.

During the treatment period, physical examinations should be performed prior to dosing. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital sign measurements (ie, systolic and diastolic BP [mm Hg], heart rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), weight (kg), and height (cm) will be obtained at the visits designated in the SoA (Section 1.3) by a validated method.

- BP and heart rate will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) shows an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

- Between clinic visits, and in particular for phone or virtual visits at C1D8 and C3D8, BP may be measured. If the participant does not return to the study site for this BP measurement, BP may be measured, for example, at home or at a local pharmacy, and the results will be reviewed with the investigator or designee. The investigator/site may provide a diary as a tool to aid the participant in collecting BP evaluations between clinic visits. The Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an onsite BP retest, or other clinically appropriate intervention(s).

8.3.3 Electrocardiograms

ECGs will be obtained as designated in the SoA (Section 1.3). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. The Fridericia correction method for calculating QTc will be used.

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

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Appendix 3) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the appropriate CRF.

QTc prolongation has been seen in some lenvatinib studies. Monitor ECGs every cycle (as specified in the SoA) in participants with congenital long QT syndrome, CHF, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Refer to the lenvatinib IB.

8.3.4 Echocardiogram or Multiple Gated Acquisition Scan

A MUGA scan (using technetium-based tracer) or an ECHO will be performed to assess LVEF as designated in the SoA (Section 1.3). MUGA or ECHO scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based on institutional reports.

Country-specific requirements are noted in Appendix 7.

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

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

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the timing in the Laboratory Manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days (or 90 days if considered an SAE) after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.
- CBC with differential and clinical chemistry results must be reviewed before administration of study intervention. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting study intervention.

8.3.6 Pregnancy Testing

Pregnancy testing ([urine or serum] as required by local regulations) should be conducted according to Section 1.3 (SoA) and at the end of relevant systemic exposure for all arms (120 days after last dose of pembrolizumab, 30 days after last dose of lenvatinib, or 180 days after last dose of chemotherapy, whichever occurs last).

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Pregnancy testing ([urine or serum] as required by local regulations) should be conducted at monthly intervals during intervention.
- Pregnancy testing must be performed by WOCBP at the study Discontinuation Visit and consistent with the contraception requirements in Section 5.1.
- 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.

Country-specific requirements are noted in Appendix 7.

8.3.7 Eastern Cooperative Oncology Group Performance Scale

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

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before 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 intervention allocation/randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of allocation/intervention randomization through 120 days after cessation of pembrolizumab or 30 days after cessation of lenvatinib, or 180 days after chemotherapy, whichever occurs last, must be reported by the investigator. If the participant initiates new anticancer therapy after discontinuation of study intervention, the time for reporting pregnancies and exposure during breastfeeding is reduced to 30 days after cessation of study intervention.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.
- Country-specific requirements are listed in Appendix 7.

Investigators are not obligated to actively seek AEs or SAEs 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 the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

Once a participant has been consented for the extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 13.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 13 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified AE Collection Period**	**Reporting Period: After the Protocol-specified AE Collection Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
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 Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor
SAE	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.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Potential DILI events meeting biochemical criteria of Hy's Law (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report - regardless of suspected etiology - to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – requires regulatory reporting	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
New Cancer (that is not the cancer under study)	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)
AE=adverse event; DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; OME=other important medical event; SAE=serious adverse event.				

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. SAEs and other reportable safety events, including potential DILI events meeting biochemical criteria of Hy's Law, pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). The investigator will also make every attempt to follow nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), 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 an 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 spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

Efficacy endpoints as outlined in Section 3 will not be reported to the Sponsor as AEs/SAEs.

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

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

8.4.7 Events of Clinical Interest

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

ECIs for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5; lenvatinib overdose without an associated AE is not considered an ECI.

- All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential DILI events are defined as:
  - An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and,
  - An elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and,
  - At the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN,

determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on 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 Study File Binder (or equivalent).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for

- Pembrolizumab: any dose of 1000 mg or greater
- Lenvatinib: any dose above the protocol-prescribed dose if associated with an AE

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in participants receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies

at the recommended dose for differentiated thyroid cancer, RCC, and HCC. No specific information is available on the treatment of overdose of pembrolizumab or lenvatinib.

All reports of pembrolizumab overdose with and without an AE and all reports of lenvatinib overdose with an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

Reports of pembrolizumab overdose without any associated clinical symptoms or abnormal laboratory results, should be reported using the terminology "accidental or intentional overdose without adverse effect."

CAPOX/mFOLFOX6: ≥10% over the prescribed dose should be reported as detailed in Section 10.3.1 (Note: an overdose is not considered an ECI).

8.6 Pharmacokinetics

8.6.1 Plasma Collection for Lenvatinib

Plasma samples will be collected as specified in the SoA (Section 1.3). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the Laboratory Manual.

Plasma samples will be collected from all participants in the Induction Phase and may only be stored at this time. Plasma concentrations of lenvatinib when co-administered with pembrolizumab and chemotherapy will be measured. Lenvatinib may be analyzed using a population PK approach.

If at some point during the study, prospective PK blood sample collection is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued, and sites will be notified accordingly.

8.6.2 Serum Collection for Pembrolizumab

To evaluate pembrolizumab immunogenicity and exposure when administered in combination with lenvatinib and chemotherapy, sample collections for analysis of ADAs and PK are currently planned as specified in the SoA (Section 1.3). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of pembrolizumab ADA and PK samples will be provided in the Laboratory Manual.

Serum samples for pembrolizumab PK and ADA collected may only be stored at this time. Further analysis may be performed if required and reported separately if conducted. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

8.7 Pharmacodynamics

Not applicable.

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[redacted]

8.11 Visit Requirements

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

8.11.1 Screening

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

Documented informed consent must be provided prior to performing any protocol-specific procedure. Results of a test performed prior to the participant providing documented informed 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 after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.11.2 Safety Run-in

A 21-day Safety Run-in period will enroll approximately12 participants as described in Section 4.1.

8.11.3 Treatment Period Visit

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1, Section 8.2, and Section 8.3.

In the Safety Run-in Phase (Part 1), approximately 12 participants who are eligible for study participation will receive unblinded, open-label treatment with either lenvatinib plus pembrolizumab plus CAPOX or lenvatinib plus pembrolizumab plus mFOLFOX6 chemotherapy.

In the Induction Phase, participants who are eligible for study participation will be assigned to receive unblinded, open-label treatment with lenvatinib plus pembrolizumab plus CAPOX or mFOLFOX6 chemotherapy (Arm 1), or CAPOX or mFOLFOX6 only (Arm 2) chemotherapy.

In the Consolidation Phase, participants will receive lenvatinib plus pembrolizumab only (Arm 1) or CAPOX or mFOLFOX6 (Arm 2).

Lenvatinib will be taken orally once daily, and pembrolizumab will be given by IV infusion on Day 1 of each 42-day cycle, as outlined in Section 8.1.8. CAPOX or mFOLFOX6 chemotherapy will be administered on a 3-weekly or 2-weekly schedule, respectively.

Participants will be scheduled to visit the clinic as follows:

- For lenvatinib plus pembrolizumab plus CAPOX, study visits will occur on Days 1, 15, 22 and 36 of Cycle 1, Days 1 and 22 of Cycle 2; Days 1, 15 and 22 of Cycle 3, and Day 1 and Day 22 of Cycles 4-18. Participants will be contacted by telephone/virtually on Cycle 1, Day 8, Cycle 1 Day 29, and Cycle 3 Day 8.
- For lenvatinib plus pembrolizumab plus mFOLFOX6, study visits will occur on Days 1, 15, and 29 of Cycle 1 and Cycle 2; Days 1, 15 and 22 of Cycle 3, and Day 1 and Day 22 of Cycles 4-18. Participants will be contacted by telephone/virtually on Cycle 1, Day 8 and Cycle 3 Day 8.
- For CAPOX only, study visits will occur on Day 1 and Day 22 of every cycle.
- For mFOLFOX6 only, study visits will occur on Day 1, Day 15 and Day 29 of every cycle.

Due to the differences in visit schedule, once randomized, the participants cannot switch between chemotherapy backbones.

Participants may be seen more frequently, if clinically indicated. Tumor imaging and response assessment will occur every 6 weeks from the day of randomization.

Study interventions will continue until reaching a discontinuation criterion (Section 7.1), examples of which include disease progression which is radiographically documented and verified by BICR per RECIST 1.1, unacceptable toxicity; intercurrent illness that prevents further administration of treatment; investigator's decision to withdraw treatment; participant withdrawal of consent; pregnancy; noncompliance with study intervention or procedure

requirements; administrative reasons requiring cessation of treatment; or, for CAPOX, mFOLFOX6, and pembrolizumab ONLY, treatment completion (18 cycles of pembrolizumab; maximum cycles of CAPOX/mFOLFOX6 as per local standard). There is no treatment duration limit for lenvatinib.

Completion of pembrolizumab Q6W consists of 18 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 4 cycles (at least 24 weeks) of pembrolizumab, receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for Second Course Treatment described in Section 6.6.6.

8.11.4 Discontinued Participants Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures, and any additional Safety Follow-up procedures should be performed.

Visit requirements are outlined in the SoA. Additional details regarding participant withdrawal and discontinuation are presented in Section 8.1.9.

8.11.5 Posttreatment

8.11.5.1 Safety Follow-up Visit

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

Participants who are eligible for retreatment with pembrolizumab may have up to 2 Safety Follow-up Visits, 1 after the Initial Treatment or First Course and 1 after Second Course.

8.11.5.2 Efficacy Follow-up Visit(s)

Note: As of Amendment 8, this section is no longer applicable. Participants in Efficacy Follow-up prior to the initiation of Amendment 8 will stop efficacy assessments and be discontinued from the study and should continue with tumor imaging per local standard of care. AEs and other reportable safety events will be reported and followed as described under Section 8.4.

Participants who discontinue study intervention for a reason other than progressive disease will begin Efficacy Follow-up and should be assessed as outlined in the SoA (Section 1.3) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, or end of study, or if the participant begins retreatment with pembrolizumab, as detailed in Section 6.6.6. Information regarding poststudy anticancer treatment will be collected if new treatment is

initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.6.6 will move from Efficacy Follow-up to Second Course when they experience disease progression. Details are provided in the SoA (Section 1.3) for retreatment with pembrolizumab.

8.11.5.3 Survival Follow-up Contacts

Note: As of Amendment 8, this section is no longer applicable. Participants in Survival Follow-up prior to initiation of Amendment 8 are considered to have completed the study and should have a final survival contact; these participants will no longer be contacted for survival information. AE, SAE, and other reportable safety events will be reported and followed as described under Section 8.4.

Participant survival follow-up status will be assessed 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:

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

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

8.11.6 Vital Status

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

If a participant withdraws consent, vital status (survival information) may be obtained by review of public records, in accordance with local regulations. If a participant is lost to follow-up, vital status (survival information) can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun but prior to the conduct of any planned analysis, 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 the conduct of any planned analysis, will be documented in an sSAP and referenced in the CSR for the study. Other planned analyses (ie, those specific to the analysis of PK data and biomarker data) will be documented in separate analysis/operational plans. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Phase 3, randomized, open-label study of lenvatinib plus pembrolizumab plus chemotherapy compared with chemotherapy only in participants with locally advanced unresectable/metastatic gastroesophageal adenocarcinoma
Treatment Assignment	Part 1: Approximately 12 participants will be assigned to one of 2 treatment groups at the discretion of the investigator with ~6 participants treated per treatment group: Lenvatinib + pembrolizumab + CAPOX Lenvatinib + pembrolizumab + mFOLFOX6 Part 2: Approximately 878 participants will be randomized in a 1:1 ratio to the experimental group and the control group: Lenvatinib + pembrolizumab + CAPOX/ mFOLFOX6 CAPOX/ mFOLFOX6 Stratification factors for Part 2 are: 1) region (East Asia, North America + Western Europe versus Rest of World), 2) ECOG (0 or 1) and 3) Intended chemotherapy (CAPOX or mFOLFOX6).
Analysis Populations	Part 1 and Part 2 participants will be analyzed separately. Efficacy: ITT Safety: APaT
Primary Endpoints	Part 1: Safety and tolerability Part 2: OS PFS per RECIST 1.1 assessed by BICR
Key Secondary Endpoint	Part 2: OR per RECIST 1.1 assessed by BICR

Statistical Methods for Key Efficacy Analyses	Part 2: The primary hypotheses on PFS and OS will be evaluated by comparing the experimental group to the control group using a stratified log-rank test. The HR will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The stratified M&N method with strata weighted by sample size will be used for analysis of ORR. The study will be considered to have met its primary objective if at least 1 primary hypothesis testing is statistically significant.
Statistical Methods for Key Safety Analyses	Part 1: Descriptive summary statistics will be provided for safety endpoints by treatment as appropriate. Part 2: 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 Analyses	Part 1: No IA is planned. Participants will be closely followed for DLTs for 21 days after the first dose of study intervention. Part 2: One IA will be performed in this study. Results will be reviewed by an eDMC. Details are provided in Section 9.7. IA: Timing: to be performed after both ~494 PFS events have occurred in CPS ≥1 participants and ~8 months after the last participant randomized. Primary purpose: efficacy analysis for ORR, PFS and OS. Final analysis (FA): Timing: to be performed after both ~537 deaths have occurred in CPS ≥1 participants and ~18 months after the last participant randomized. Primary purpose: efficacy analysis for OS. Note for IA and FA, if the events accrue slower than expected, the Sponsor may conduct the analysis with up to 3 additional months of follow-up than the follow-up as described above, or when the specified number of events is observed, whichever occurs first.
Multiplicity	Part 1: No multiplicity adjustment is planned. Part 2: The overall type I error over the primary endpoints (PFS and OS) and the key secondary endpoint (ORR) is strongly controlled at 2.5% (one-sided), with initially 0% allocated to ORR, 0.7% to PFS and 1.8% to OS in CPS ≥1 participants. By using the graphical approach of Maurer and Bretz, if one hypothesis is rejected, the alpha will be shifted to other hypotheses [Maurer, W. and Bretz, F. 2013].

Sample Size and Power	Part 1: Approximately 12 participants will be enrolled. Part 2: Approximately 878 participants are planned to be enrolled. The actual overall sample size of the study for all participants is 880. The sample size for CPS ≥1 participants is approximately 680. For OS, there will be ~537 deaths in CPS ≥1 participants at the OS final analysis. With 537 deaths, the study has ~85% power for detecting a hazard ratio (HR) of 0.76 at an initially assigned 1.8% (one-sided) significance level. For PFS, there will be ~494 events in CPS ≥1 participants at IA. With 494 PFS events, the study has ~94% power for detecting a HR of 0.7 at an initially assigned 0.7% (one-sided) significance level. For ORR, with sample size of 680 in CPS ≥1 participants at IA, the study has ~98.5% power for detecting a 20-percentage point difference in ORR (57% versus 37%) at a significance level of 0.1001% (if H2 rejected only). The median PFS of 6 months and the median OS of 11.5 months, and the ORR of 37% in the control group for the sample size estimations are based on CPS ≥1 participants treated with the standard care of chemotherapy from KN062 (the first line of HER-2 negative, previously untreated, unresectable or metastatic gastric/GEJ adenocarcinoma).

9.2 Responsibility for Analyses/In-house Blinding

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

Part 1 of the study is being conducted as an open-label study, ie, participants, investigators, and Sponsor personnel will be aware of treatment assignments after each participant is enrolled and treatment is assigned. Safety data will be closely monitored for 21 days after the first dose of study intervention.

Although Part 2 of the study is open-label, analyses or summaries generated by randomized intervention assignment, or actual treatment received will be limited and documented. Further documentation will be provided in the sSAP. In addition, independent radiologists will perform the central imaging review without knowledge of treatment assignments.

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

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

9.4.1.1 Primary

Overall Survival (OS)

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

Progression-free Survival (PFS) per RECIST 1.1 Assessed by BICR

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

9.4.1.2 Secondary

Objective Response per RECIST 1.1 by BICR

The OR is defined as a confirmed CR or a PR per RECIST 1.1 as assessed by BICR (note: only CR or PR prior to a curative surgical resection will be used among participants with curative surgical resection).

Duration of Response (DOR) per RECIST 1.1 by BICR

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

9.4.1.3 Exploratory

PFS and OR per RECIST 1.1 as assessed by the investigator.

9.4.2 Safety Endpoint

DLTs for Part 1 are defined in Table 2. Other safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, and vital signs.

9.4.3 Patient-reported Outcome (PRO) Endpoint

Exploratory PRO endpoints (eg, score change from baseline over time), which include EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D-5L scores, are described in Section 3 and Section 4.2.1.3. Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the population for efficacy analysis other than DOR. All randomized participants, whether treatment was administered, will be included in this

population. Participants will be included in the treatment group to which they are randomized. The DOR analysis will be based on the population of responders (participants that achieved complete or PR).

Part 1 participants will be excluded from all Part 2 efficacy analyses and therefore will not contribute to the analyses to assess the primary/secondary objectives of Part 2.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the study intervention group to which they are randomized. Participants who receive incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received.

Any participant who receives the incorrect study intervention for 1 or more cycles but receives the correct study intervention for the remaining cycles will be analyzed according to the participant's randomized treatment group, and a narrative will be provided for any events that occur during the cycle for which the participant was incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Participants in Part 1 and Part 2 will be analyzed separately.

9.5.3 PRO Analysis Populations

The PRO analyses are based on the PRO FAS population, defined as all randomized participants who have at least one PRO assessment available for the specific endpoint and have received at least one dose of the study intervention. Participants will be analyzed in the treatment group to which they are randomized.

PRO analyses will be performed in Part 2 participants only.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8, Multiplicity. Nominal p-values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity.

9.6.1 Statistical Methods for Efficacy Analyses

Efficacy analyses will be performed in Part 2 participants only. This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified M&N method. If there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP prior to the database lock for any efficacy IA or final analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

Response or progression in the Second Course phase will not count toward the PFS, OR, and DOR analyses in this study.

9.6.1.1 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR). The HR and its 95% CI from the Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the last known alive date.

9.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment groups. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Because disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered as a confirmed PD event. To evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 1 primary and 2 sensitivity analyses with a different set of censoring rules will be performed.

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer therapy prior to documented progression will be censored at the last disease assessment prior to the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

To evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers discontinuation of treatment due to reasons other than CR or initiation of new anticancer treatment, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

The censoring rules for primary and sensitivity analyses are summarized in Table 14.

Table 14 Censoring Rules for Primary and Sensitivity Analyses of PFS

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

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
PD=progressive disease; PFS=progression-free survival; the curative surgical resection (details in Section 6.5.3) will be excluded for the new anticancer therapy.			

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

9.6.1.3 Objective Response Rate

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

The point estimate of ORR will be provided by treatment group, together with 95% CI using exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

9.6.1.4 Duration of Response

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a CR or PR will be included in this analysis. For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding subjects who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules are summarized in Table 15.

Table 15 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (nonevent)
No progression nor death, new anticancer therapy[a] initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (nonevent)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (nonevent)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)

A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

[a] new anticancer therapy: excluding curative surgical resection.

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

Table 16 summarizes the primary analysis approach for key efficacy endpoints.

Table 16 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method [a]	Analysis Population	Missing Data Approach
Primary Endpoints			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥1 and all participants)	Censored at the last known alive date
PFS per RECIST 1.1 by BICR	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥1 and all participants)	Primary censoring rule Sensitivity analysis 1 Sensitivity analysis 2 (More details are provided in Table 14, Censoring Rules for Primary and Sensitivity Analyses of PFS)

Endpoint	Statistical Method [a]	Analysis Population	Missing Data Approach
Key Secondary Endpoint			
Objective response per RECIST 1.1 by BICR	Test and Estimation: Stratified M&N method with sample size weight	ITT (CPS ≥1 and all participants)	Participants without assessments are considered nonresponders and conservatively included in the denominator

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

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

The strategy to address multiplicity issues with regard to multiple endpoints and interim analyses is described in Section 9.7 (Interim Analyses) and Section 9.8 (Multiplicity).

9.6.2 Statistical Methods for Safety Analyses

9.6.2.1 Overall Safety Assessment

Part 1: Participants will be closely followed for DLTs for 21 days after the first dose of study intervention. Descriptive summary statistics (eg, counts, percentages) will be provided for DLTs by treatment as appropriate. Other safety and tolerability will also be assessed by clinical review of all relevant parameters.

Part 2: The primary safety analyses will include only events that occur prior to Second Course Treatment.

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, a drug-related AE, an SAE, a serious drug-related AE, a Grade 3 to 5 AE, a drug-related Grade 3 to 5 AE, a discontinuation from study intervention due to an AE, and an AE resulting in death. Point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with the event will be provided based on the criteria described below.

Point estimate and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided for AEs that occur in at least 10% of participants in any treatment group. The threshold of at least 10% of participants was chosen 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, difference in the percentage of participants with specific Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) will also be summarized by point estimate and 95% CIs.

CIs for between treatment group differences will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985]. 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.

9.6.2.2 Assessment of Safety Topics of Special Interest

AEs that are immune-mediated or potentially immune-mediated will be evaluated separately. These events have been characterized consistently throughout the pembrolizumab clinical development program. Point estimates and 95% CIs for between-group difference is not expected to add value to the safety evaluation, and hence only number and percentage of participants with such pembrolizumab AEOSI will be provided, as well as the number and percentage of participants with corticosteroids administration to treat an AEOSI. Summary statistics will be provided for the analysis of time from first dose to the onset of an AEOSI. Similar approach will be applied to CSAE for lenvatinib.

Table 17 summarizes the analysis strategy for safety endpoints in this study.

Table 17 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% between-group CI (Graphical display)
Overall Safety Assessment	Specific AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
	Specific Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Specific serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Any AE	X	
	Any Grade 3-5 AE	X	
	Any serious AE	X	
	Any drug-related AE	X	
	Any serious and drug-related AE	X	
	Any Grade 3-5 and drug-related AE	X	
	Discontinuation study treatment due to AE	X	
	AE that resulted in death	X	
	Change from Baseline Results (lab toxicity shift, vital signs)	X	

Analysis Part	Safety Endpoint	Descriptive Statistics	95% between-group CI (Graphical display)
Assessment of safety topics of special interest	Pembrolizumab AEOSI	X	
	Lenvatinib CSAE	X	

AE=adverse event; CI=confidence interval; SAE=serious adverse event; AEOSI=adverse event of special interest; CSAE=clinically significant adverse event; X = results will be provided.

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

PRO analyses will be performed in Part 2 participants only. Details of PRO analyses will be described in the sSAP.

9.6.4 Summaries of Demographic and Baseline Characteristics

Part 1: The relevant demographics and baseline characteristics will be summarized. The number and percentage of participants screened, randomized, and the primary reasons for screening failure and discontinuation will be displayed.

Part 2: The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, and the primary reasons for screening failure and discontinuation will be displayed.

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

9.7 Interim Analyses

Part 1

In this open-label Safety Run-in Phase, participants will be closely followed for DLTs for 21 days after the first dose of study intervention. If 3 or more DLTs occur in either chemotherapy backbone treatment group during this Safety Run-in, enrollment to Part 2 may be delayed to further examine safety data and consider study design changes.

Part 2

An eDMC will review the unblinded efficacy results and accumulating safety data at planned interim analysis. Treatment-level results of the interim analysis will be provided by the unblinded statistician to the eDMC. The eDMC responsibilities and review schedules will be outlined in the DMC Charter. The recommendations of the eDMC will be communicated to the EOC. If the eDMC recommends modifications to the design of the protocol or

discontinuation of the study, the EOC, and possibly other limited numbers of additional Sponsor personnel, may be unblinded to results at the treatment level to act on these recommendations. Participant-level unblinding to support regulatory filing, should this occur before the end of the study, will be restricted to a designated Sponsor team, who will have no other responsibilities associated with the study. The extent to which individuals are unblinded with respect to the results will be documented.

Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the eDMC Charter.

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 analysis.

9.7.1 Efficacy Interim Analysis

One interim analysis is planned in addition to the final analysis for this study. For the interim and final analyses, all randomized participants will be included. Results of the interim analysis will be reviewed by the eDMC. The timing and the purpose of the interim and final analyses are summarized in Table 18. Type I error control for the efficacy analyses as well as efficacy bounds are described in Section 9.8.

Table 18 Summary of Interim and Final Analyses Strategy for Efficacy

Analyses	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA	Both ~494 PFS events have occurred in CPS ≥1 participants and ~8 months after the last participant randomized. Approximately, 450 OS events in CPS ≥1 participants are expected with this trigger.	~31 months	Efficacy analysis for ORR, PFS and OS in CPS ≥1 and all participants. This is the final analysis of ORR and PFS, and the IA of OS.
Final Analysis	Both ~537 deaths have occurred in CPS ≥1 participants and ~18 months after the last participant randomized.	~41 months	Efficacy analysis for OS in CPS ≥1 and all participants. This is the final analysis of OS.

IA=interim analysis; CPS=combined positive score; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Note for IA and FA: if the events accrue slower than expected, the Sponsor may conduct the analysis with up to 3 additional months of follow-up than the follow-up as described above, or when the specified number of events is observed, whichever occurs first.

9.7.2 Safety Interim Analysis

In Part 2, the eDMC will be responsible for periodic interim safety reviews, as specified in the DMC Charter. Interim safety analysis will also be performed at the time of interim

efficacy analysis. In this open-label study, participants will be actively monitored at ongoing basis. Because there is limited experience in the full combination of pembrolizumab with lenvatinib and CAPOX or mFOLFOX6, there will be an independent first safety review by an eDMC after at least 20 participants in the experimental arm have completed 2 cycles of induction therapy.

9.8 Multiplicity

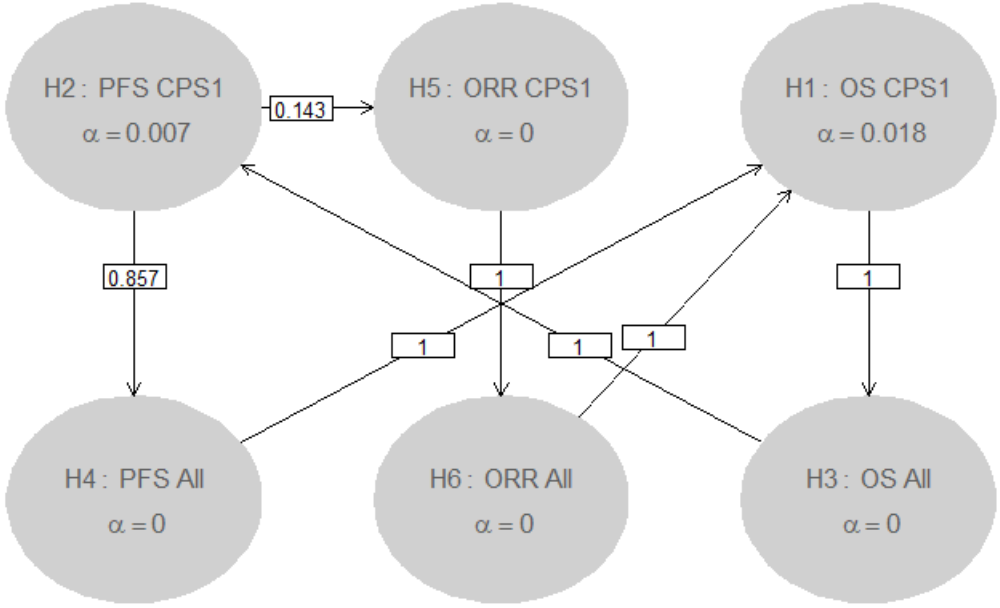
Part 1

No multiplicity adjustment is needed because there is no hypothesis testing.

Part 2

The study uses an extension of the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses while making the interim and final analysis timing more flexible. According to the Maurer and Bretz approach, study hypotheses may be tested in a group sequential fashion, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 7 shows the initial 1-sided alpha allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

Figure 7 Multiplicity Graph for Type I Error Control of Study Hypotheses



CPS=combined positive score; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

The extended graphical method spends alpha as a function of the minimum of the actual event information fraction and the expected event information fraction. This ensures that the actual spending will be no more aggressive than the planned spending while at the same time ensuring that not all alpha is spent prior to final planned event counts.

9.8.1 OS Hypotheses

Figure 7 shows that initial alpha=0.018 will be allocated to the OS hypothesis in CPS ≥1 participants (H1) and no initial alpha will be allocated the OS hypothesis in all participants (H3). According to Figure 7, H1 may also be tested at alpha=0.023999 (H2 and H4 rejected), 0.019001 (H2, H5, and H6 rejected), and 0.025 (H2, H5, H4, and H6 rejected). As an example, Table 19 shows the bounds and boundary properties for H1, when tested at initial alpha=0.018 and full alpha=0.025, derived using a Lan-DeMets O'Brien-Fleming spending function based on the predicted number of events, at the planned time of analysis.

The bounds provided in Table 19 are based on the assumption that the expected events at IA and FA are 450 and 537 in CPS ≥1 participants, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at the IA and leave reasonable alpha for the final analysis, the minimum alpha spending strategy will be adopted. At the IA, the information fraction used in Lan-DeMets spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically,

In the scenario that the events accrue slower than expected and the observed number of events is less than the expected events at a given analysis, the information fraction will be calculated as the observed number of events at the IA over the target number of events at FA.

In the scenario that the events accrue faster than expected and the observed number of events exceed the expected number of events at a given analysis, then the information fraction will be calculated as the expected number of events at the IA over the target number of events at FA. For example, at IA, if 470 OS events have occurred (ie, more than the expected 450 OS events), the alpha spending at IA will be according to the expected information fraction (450/537= 84%) instead of the actual information fraction (470/537 = 88%).

The final analysis timing is driven by OS events from the CPS ≥1 participants. The final analysis will use the remaining Type I error that has not been spent at the IA. The event counts for all analyses will be used to compute correlations.

Of note, while the information fraction used for alpha spending calculation will be the minimum of the actual information fraction and the expected information fraction, the correlations required for deriving the bounds will still be computed using the actual information fraction based on the observed number of events at each analysis over the target number of events at FA.

The minimum spending approach assumes timing is not based on any observed Z-value and thus the Z test statistics used for testing conditioned on timing are multivariate normal. Given the probabilities derived with the proposed spending method, the correlations based on actual event counts are used to compute bounds that control the Type I error at the specified alpha level for a given hypothesis conditioned on the IA timing. Because this is true regardless of what is conditioned on, the overall Type I error for a given hypothesis unconditionally is controlled at the specified level. By using more conservative spending early in the study, power can be retained to detect situations where the treatment effect may be delayed.

Table 19 Efficacy Boundaries and Properties for OS Analysis in CPS ≥1 Participants

Analysis	**Value**	**α=0.018**	**α=0.025**
IA : 84%[a]	Z	2.3350	2.1880
N: 680	p (1-sided)[b]	0.0098	0.0143
Events: 450	HR at bound[c]	0.8022	0.8135
Month: 31	P(Cross) if HR=1[d]	0.0098	0.0143
	P(Cross) if HR=0.76[e]	0.7182	0.7657
Final	Z	2.1660	2.0360
N: 680	p (1-sided)[b]	0.0152	0.0209
Events: 537	HR at bound[c]	0.8294	0.8388
Month: 41	P(Cross) if HR=1[d]	0.0180	0.0250
	P(Cross) if HR=0.76[e]	0.8541	0.8825

CPS=combined positive score; HR=hazard ratio; IA=interim analysis
a Percentage of expected number of events at the IA over the expected number at final analysis.
b Nominal alpha for group sequential testing.
c HR at bound is the approximate HR required to reach an efficacy bound.
d Probability of crossing a bound under the null hypothesis.
e Probability of crossing a bound under the alternative hypothesis.

OS hypothesis in all participants (H3) does not have initial alpha assignment but may receive alpha stepped down from OS hypothesis in CPS ≥1 participants (H1). H3 may be tested at alpha= 0.018 (H1 rejected), 0.023999 (H1, H2, and H4 rejected), 0.019001 (H1, H2, H5, and H6 rejected), and 0.025 (H1, H2, H5, H4, and H6 rejected). As an example, Table 20 shows the bounds and boundary properties for H3, when tested at alpha=0.018 and full alpha=0.025, derived using a Lan-DeMets O'Brien-Fleming spending function based on the predicted number of events at the planned time of analysis.

Table 20 Efficacy Boundaries and Properties for OS Analysis in All Participants

Analysis	**Value**	**α=0.018**	**α=0.025**
IA: 84%[a]	Z	2.3350	2.1870
N: 880	p (1-sided)[b]	0.0098	0.0144
Events: 588	HR at bound[c]	0.8247	0.8349
Month: 31	P(Cross) if HR=1[d]	0.0098	0.0144
	P(Cross) if HR=0.80[e]	0.6452	0.6984
Final	Z	2.1660	2.0360
N: 880	p (1-sided)[b]	0.0152	0.0209
Events: 701	HR at bound[c]	0.8491	0.8575
Month: 41	P(Cross) if HR=1[d]	0.0180	0.0250
	P(Cross) if HR=0.80[e]	0.7969	0.8326

HR=hazard ratio; IA=interim analysis; OS=overall survival.
a Percentage of expected number of events at the IA over the expected number at final analysis.
b Nominal alpha for group sequential testing.
c HR at bound is the approximate HR required to reach an efficacy bound.
d Probability of crossing a bound under the null hypothesis.
e Probability of crossing a bound under the alternative hypothesis.

9.8.2 PFS Hypotheses

Figure 7 shows that initial alpha=0.007 will be allocated to the PFS hypothesis in CPS ≥1 participants (H2) and no initial alpha will be allocated the PFS hypothesis in all participants (H4). According to Figure 7, H2 may also be tested at alpha= 0.025 (H1and H3 rejected). As an example, Table 21 shows the bounds and boundary properties for H2, when tested at initial alpha=0.007 and full alpha=0.025, derived using a Lan-DeMets O'Brien-Fleming spending function based on the predicted number of events, at the planned time of analysis.

The bounds provided in Table 21 are based on the assumption that the expected number of events at IA is 494 in CPS1 participants.

Table 21 Efficacy Boundaries and Properties for PFS Analysis in CPS ≥1 Participants

Analysis	**Value**	**α=0.007**	**α=0.025**
IA	Z	2.4573	1.96
N: 680	p (1-sided)[a]	0.007	0.025
Events: 494	HR at bound[b]	0.8016	0.8383
Month: 31	P(Cross) if HR=1[c]	0.007	0.025
	P(Cross) if HR=0.7[d]	0.9352	0.9778

CPS=combined positive score; HR=hazard ratio; IA=interim analysis.
a Nominal alpha for group sequential testing.
b HR at bound is the approximate HR required to reach an efficacy bound.
c Probability of crossing a bound under the null hypothesis.
d Probability of crossing a bound under the alternative hypothesis.

PFS hypothesis in all participants (H4) did not have initial alpha assignment but will receive alpha stepped down from PFS hypothesis in CPS ≥1 participants (H2). H4 may be tested at alpha= 0.005999 (H2 rejected), 0.021425 (H1, H2, and H3 rejected), and 0.025 (H1, H2, H3, H5, and H6 rejected). As an example, Table 22 shows the bounds and boundary properties for H4, when tested at alpha=0.005999 and full alpha=0.025, derived using a Lan-DeMets O'Brien-Fleming spending function based on the predicted number of events at the planned time of analysis.

Table 22 Efficacy Boundaries and Properties for PFS Analysis in All Participants

Analysis	**Value**	**α=0.005999**	**α=0.025**
IA	Z	2.5122	1.96
N: 880	p (1-sided) [a]	0.005999	0.025
Events: 644	HR at bound [b]	0.8204	0.8569
Month: 31	P(Cross) if HR=1[c]	0.005999	0.025
	P(Cross) if HR=0.73[d]	0.9316	0.9792

HR=hazard ratio; IA=interim analysis; PFS=progression-free survival.
a Nominal alpha for group sequential testing.
b HR at bound is the approximate HR required to reach an efficacy bound.
c Probability of crossing a bound under the null hypothesis.
d Probability of crossing a bound under the alternative hypothesis.

If H1 and H3 with regard to OS hypotheses is either rejected at the IA or rejected at final analysis, the reallocation strategy allows retesting of PFS based on the data for the PFS final analysis at IA.

9.8.3 ORR Hypotheses

No initial alpha will be allocated for the ORR hypothesis in CPS ≥1 participants (H5) or in all participants (H6). H5 will receive alpha stepped down from PFS hypothesis in CPS ≥1 participants (H2). H5 may be tested at alpha= 0.001001 (H2 rejected), 0.003575 (H1, H2 and H3 rejected) and 0.025 (H1, H2, H3 and H4 rejected).

H6 will receive alpha stepped down from ORR hypothesis in CPS ≥1 participants (H5). H6 may be tested at alpha= 0.001001 (H2 and H5 rejected), 0.003575 (H1, H2, H3 and H5 rejected) and 0.025 (H1, H2, H3, H4 and H5 rejected). If H1 and H3 with regard to OS hypotheses is either rejected at the IA or rejected at final analysis, the reallocation strategy allows retesting of PFS based on the data for the PFS final analysis at IA, and then retesting of ORR based on the data from the ORR final analysis at IA if H2 rejected.

The statistical power at an alpha-levels of 0.001001 and 0.025 (one-sided) as well as the approximate treatment difference required to reach the bound in terms of ORR difference are shown in Table 23.

Table 23 Statistical Power and Approximate ORR Difference Required to Show Efficacy for ORR at IA

Sample Size	Expected treatment difference	Alpha	Observed Difference Required to Show Efficacy	Power
CPS ≥1 (N=680)	20%	0.001001 0.025	~11.8% ~7.5%	98.5% 99.9%
All (N=880)	15%	0.001001 0.025	~10.4% ~6.6%	92.0% 99.5%
CPS=combined positive score; IA=interim analysis; ORR=overall response rate.				

9.8.4 Safety Analyses

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

9.9 Sample Size and Power Calculations

The enrollment is complete.

Part 1

Approximately 12 subjects will be enrolled in Part 1. The sample size is determined based on clinical considerations to rule out dose-limiting toxicities.

Part 2

The study will randomize participants in a 1:1 ratio into the experimental group and the control group. PFS and OS are primary endpoints for the study, with ORR as the key secondary endpoint. Approximately 878 participants are planned to be enrolled. The actual overall sample size of the study for all participants is 880. The sample size for CPS ≥1 participants is approximately 680. Power and IA calculations were performed using the gsDesign R package.

9.9.1 Overall Survival

There will be ~537 deaths at the OS final analysis in CPS ≥1 participants. With 537 deaths, the study has ~85% power for detecting an HR of 0.76 at an initially assigned 0.018 (one-sided) significance level.

If H1 (ie, OS endpoint in CPS ≥1 participants) is rejected, alpha=0.018 can be passed from H1 to H3 (OS endpoint in all participants). There will be ~701 deaths in all participants at the final OS analysis. With 701 deaths, the study has ~80% power for detecting an HR of 0.80 at a significance level of 0.018 (1-sided).

The sample size (number of participants) calculations are based on the following assumptions: (1) the actual enrollment period is 22 months, and the ramp-up period of enrollment is 6 months; (2) the duration of OS follow exponential distribution; (3) median OS is 11.5 months in the control group and the true HR are 0.76 in CPS ≥1 participants and 0.80 in all participants; (4) the annual dropout rate is 1% for OS endpoint. The median OS in the control group is based on CPS ≥1 participants treated with the standard care of chemotherapy from KN062 (the first line of HER-2 negative, previously untreated, unresectable or metastatic gastric/GEJ adenocarcinoma).

9.9.2 Progression-free Survival

There will be ~494 events at the PFS final analysis in CPS ≥1 participants. With 494 events, the study has ~94% power for detecting an HR of 0.7 at an initially assigned 0.007 (one-sided) significance level.

If H2 (ie, PFS endpoint in CPS ≥1 participants) is rejected, alpha=0.005999 (ie, 85.7% of the initially assigned 0.007) can be passed from H2 to H4 (PFS endpoint in all participants). There will be ~644 PFS events in all participants at the final PFS analysis. With 644 PFS

events, the study has ~93% power for detecting an HR of 0.73 at a significance level of 0.005999 (1-sided).

The sample size (number of participants) calculations are based on the following assumptions: (1) the actual enrollment period is 22 months, and the ramp-up period of enrollment is 6 months; (2) the duration of PFS follow exponential distribution; (3) median PFS is 6 months in the control group and the true HR are 0.7 in CPS ≥1 participants and 0.73 in all participants; (4) the annual dropout rate is 25% for PFS endpoint. The median PFS in the control group is based on CPS ≥1 participants treated with the standard care of chemotherapy from KN062.

9.9.3 Objective Response Rate

If H2 (ie, PFS endpoint in CPS ≥1 participants) is rejected, alpha=0.001001 can be passed from H2 to H5 (ORR endpoint in CPS ≥1 participants). There will be approximately 680 in CPS ≥1 participants at IA. With sample size of 680 in CPS ≥1 participants at IA, the study has ~98.5% power for detecting a 20-percentage point difference in ORR (57% in the experimental group versus 37% in the control group) at a significance level of 0.001001 (one-sided).

If H2 and H5 (ie, PFS and ORR endpoint in CPS ≥1 participants) are rejected, alpha=0.001001 can be passed from H5 to H6 (ORR endpoint in all participants). There will be 880 in all participants at IA. With sample size of 880 in all participants at IA, the study has ~92% power for detecting a 15-percentage point difference in ORR (52% in the experimental group versus 37% in the control group) at a significance level of 0.001001 (one-sided). The ORR in the control group is based on CPS ≥1 participants treated with the standard care of chemotherapy from KN062.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the efficacy endpoints (ORR, PFS and OS) will be estimated and plotted within each category of each subgroup. The subgroup analyses will be conducted for CPS ≥1 participants and ITT population, respectively. The following are examples of classification variables:

- Age category: (<65 versus ≥65 years)
- Sex: (female versus male)
- Race: (Asian versus non-Asian)
- Region: (East Asia, North America + Western Europe versus Rest of World)
- PD-L1: (Positive versus Negative)
- MSI status: (MSI-H versus non-MSI-H)

- ECOG status: (0 versus 1)
- Disease status (locally advanced versus metastatic)
- Primary location (Gastric Cardia versus GEJ versus Esophageal Adenocarcinoma)
- Histologic subtype (diffuse versus indeterminate versus intestinal)
- Tumor Burden: (≥median versus <median)
- Prior gastrectomy/esophagectomy: (yes versus no)
- Chemotherapy (CAPOX versus mFOLFOX6)

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the analysis population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable may not be displayed in the forest plot. The subgroup analyses for PFS and OS will be conducted using an unstratified Cox model and the subgroup analyses for ORR will be conducted using the unstratified M&N method.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in months and number of cycles or administrations, as appropriate. Summary statistics will be provided on the Extent of Exposure for the ApaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

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

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), Regulation (EU) 536/2014, the 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 (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data

protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide their 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, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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

The participant must be informed that their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

CCI

[redacted]

10.1.5 Publication Policy

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

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.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 trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 24 will be performed by the local laboratory.
- Central laboratory testing is only required if the local laboratory testing is not available.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 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 (Appendix 7).
- The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Table 24 Protocol-Required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis/Urine Dipstick[a]	Other
Hematocrit Hemoglobin Platelet count RBC indices: MCV[c] MCH[c] % reticulocytes[g] WBC count with differential (absolute or percentage): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Albumin Alkaline phosphatase ALT Amylase AST BUN or Urea[d] Carbon dioxide (CO_2 or Bicarbonate)[g] Calcium Chloride CRP (as detailed in Section 1.3) Creatinine Glucose Lipase Magnesium Phosphorus Potassium Sodium Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal) Total protein	Hemoglobin or blood Glucose pH Protein Specific gravity Ketone Microscopic examination (urinalysis), if abnormal results are noted	Follicle-stimulating hormone (FSH)[b] Pregnancy test (urine or serum)[c] Hepatitis B and C testing[e,f] HIV testing[f] PT/INR and aPTT/PTT Total T3, FT4, and TSH[h,i]

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; DNA=deoxyribonucleic acid; FT3=free triiodothyronine; FT4=free thyroxine; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; PK=pharmacokinetics; PT=prothrombin time; PTT=partial thromboplastin time; RNA=ribonucleic acid; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell; WOCBP=women of childbearing potential

a If urine dipstick is abnormal, urinalysis must be performed.
b If necessary, to check menopausal status.
c Perform on WOCBP only 24 hours for urine or 72 hours for serum before first dose. Pregnancy tests must be repeated before every cycle.
d BUN or urea (one or the other should be collected per institutional standard).
e HbsAg or HBV DNA. HCV RNA (qualitative) or HCV antibody.
f Not required unless mandated by local health authorities (Appendix 7).
g Only if available as standard of care in the region.
h After Cycle 1, participants may be dosed while thyroid function test results are pending.
i Free T3/T4 is acceptable when total T3/T4 cannot be determined.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Lenvatinib overdose without an associated adverse event is not reportable as an AE.
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
   - All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as an ECI and SAE with OME criteria in the absence of other SAE criteria within 24 hours of learning of the event.

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

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

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- 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 CTCAE, version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

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

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

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

    - Grade 4: Life-threatening consequences; urgent intervention indicated.

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

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

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their 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 they have reviewed the AE/SAE and have 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

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

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the

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

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

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

Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.5.2 Contraceptive Requirements

Female Participants

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] • Intrauterine hormone-releasing system (IUS)[c] • Nonhormonal intrauterine device (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 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 Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c. IUS is a progestin releasing IUD Note: 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.

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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Laboratory Testing

HIV Status

While the protocol does not require specific testing for HIV at Screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory HIV testing at Screening is required. This can also be performed per the discretion of the investigator, if desired.

Hepatitis B/C Status

While the protocol does not require specific testing for hepatitis B/C at Screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory hepatitis B/C testing at Screening is required. This can also be performed per the discretion of the investigator, if desired.

10.7.2 Country-Specific Requirements

10.7.2.1 France

Electrocardiogram Assessment

An ECG must be arranged before and at the end of each oxaliplatin IV infusion to monitor participants treated with oxaliplatin.

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

Inclusion Criteria

The HER2 status of the tumor must be known before the inclusion of participants in the study and only participants with a HER2 negative status can be included in this study.

Exclusion Criteria

Sites in France will perform a systematic search for dihydropyrimidine dehydrogenase deficiency for participants who are naïve to 5-FU and capecitabine. This research should be performed before any administration of 5-FU and capecitabine.

Based on study design, participants on brivudine treatment or with less than 4 weeks since last dose of brivudine should be excluded from enrollment.

Live-attenuated vaccines must not be administered for 6 months after the last chemotherapy dose.

Males should use effective contraception during treatment and at least 6 months after the last dose of 5-FU or of oxaliplatin treatment.

In the case of proteinuria ≥2 g/24 hours, lenvatinib must be interrupted until proteinuria resolves to <2 g/24 hours.

Participants with mild or moderate hepatic impairment liver function tests should be monitored every 2 weeks for the first 2 months and then follow protocol visit plan.

10.7.2.2 Argentina

Laboratory Testing

HIV testing and hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the Screening period.

WOCBP at study sites in Argentina must have a pregnancy test performed before the start of the study, throughout the study and for the duration of the poststudy contraception requirements as per SoA in Section 1.3 and Appendix 10.5. Should the study treatment be delayed for any reason, then pregnancy testing should occur at least monthly during the treatment period.

10.7.2.3 Germany

Throughout the protocol:

Legally Acceptable Representative

Persons of legal age, who are incapable of comprehending the nature, significance and implications of the clinical trial and of determining their will, are excluded from the trial at German sites; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Laboratory Testing

HIV testing, and hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the Screening period.

Exclusion Criteria

Sites in Germany will perform a systematic search for dihydropyrimidine dehydrogenase deficiency for participants who are naïve to 5-FU and capecitabine. This research should be performed before any administration of 5-FU and capecitabine.

Based on study design, participants on brivudine treatment or with less than 4 weeks since last dose of brivudine should be excluded from enrollment in CAPOX-containing regimens.

MUGA Scans (for LVEF assessment)

MUGA scans are not standard practice and are not notified to the Federal Office for Radiation Protection (BfS). Therefore, only ECHO scans will be performed at the German sites for LVEF assessment in accordance with the institution's standard practice. No MUGA scans will be performed in Germany.

10.7.2.4 United Kingdom

Laboratory Testing

Tuberculosis testing, HIV testing, and hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the Screening period.

Exclusion Criteria

Sites in United Kingdom will perform a systematic search for dihydropyrimidine dehydrogenase deficiency for participants who are naïve to 5-FU and capecitabine. This research should be performed before any administration of 5-FU and capecitabine.

Live vaccines must not be administered for 90 days after the last dose of study intervention.

Pregnancy testing must be performed by WOCBP at the study Discontinuation Visit and at the end of relevant systemic exposure; ie, 30 days after the last dose of lenvatinib, 120 days after last dose of pembrolizumab or 180 days after the last dose of chemotherapy, whichever is greater.

Contraception for male participants (as described in Inclusion Criteria 6) must be used during the intervention period and for at least 6 months after the last dose of 5-fluorouracil or of oxaliplatin.

10.7.2.5 Italy

Exclusion Criteria

Sites in Italy will perform a systematic search for dihydropyrimidine dehydrogenase deficiency for participants who are naïve to 5-FU and capecitabine. This research should be performed before any administration of 5-FU and capecitabine.

Participants on brivudine treatment or with less than 4 weeks since last dose of brivudine should be excluded from enrollment.

10.7.2.6 Peru

Laboratory Testing

HIV testing and hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the Screening period.

Justification of Inclusion of Esophageal Adenocarcinoma

Esophageal adenocarcinoma (EA) is a rare entity that is difficult to study in dedicated large randomized clinical trials due to the low prevalence. Often, participants with EA are included in esophageal cancer trials where the dominant histopathology is squamous cell carcinoma (ESCC). Clinically, participants with EA may be treated with ESCC treatment paradigms, which often include radiotherapy. Alternatively, EA may be treated per gastric adenocarcinoma (GA) treatment paradigms, which are chemotherapy-based, since the histology of EA is more closely related to GA than to ESCC.

The Sponsor acknowledges that the Phase 2 EPOC trial of lenvatinib + pembrolizumab in GA did not include participants with EA for practical reasons (low prevalence in a small study) [Kawazoe, A., et al 2020a]. However, in KN-590, a study of pembrolizumab/placebo + chemotherapy in esophageal cancer, a prespecified analysis of participants with adenocarcinoma showed a benefit of the addition of pembrolizumab to chemotherapy with an HR = 0.74 (95% CI: 0.54, 1.02) that was similar to that seen in the ITT population [HR=0.73 (95% CI: 0.62, 0.0.86; $p< 0.0001$)] [Sun, J. M., et al 2021]. Based on the results of KN-590, pembrolizumab is now approved in the United States and several other countries in combination with chemotherapy for the first-line treatment of locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma.

In this LEAP-015 study, the Sponsor seeks to establish the approach for EA participants to be treated in line with GA participant treatment paradigms based on their similar histopathology. The Sponsor believes that the supportive data from the Phase 1b/2 study in upper GI adenocarcinoma participants warrant inclusion of these participants on our study.

10.7.2.7 Ireland

As per clinical practice in Ireland, HIV and Hep B/C testing is required for all participants.

10.7.2.8 Russia

Inclusion Criteria

The HER2 status of the tumor must be known before the inclusion of participants in the study and only participants with a HER2 negative status can be included in this study.

10.7.2.9 China

Inclusion Criteria

The HER2 status of the tumor must be known before the inclusion of participants in the study and only participants with a HER2 negative status can be included in this study.

10.7.2.10 Japan

Background chemotherapy

For 5-FU (mFOLFOX6), in addition to the 500 mg/10 mL or 250 mg/10 mL vials, 1,000 mg/20 mL vials may also be used.

Study Intervention(s)

Capecitabine, oxaliplatin, 5-FU and levoleucovorin used in this study is categorized as "product(s) used in the clinical trial other than test product(s)" in Japan local regulation.

10.8 Appendix 8: Management of Hypertension

Figure 8 Management of Hypertension – INDUCTION

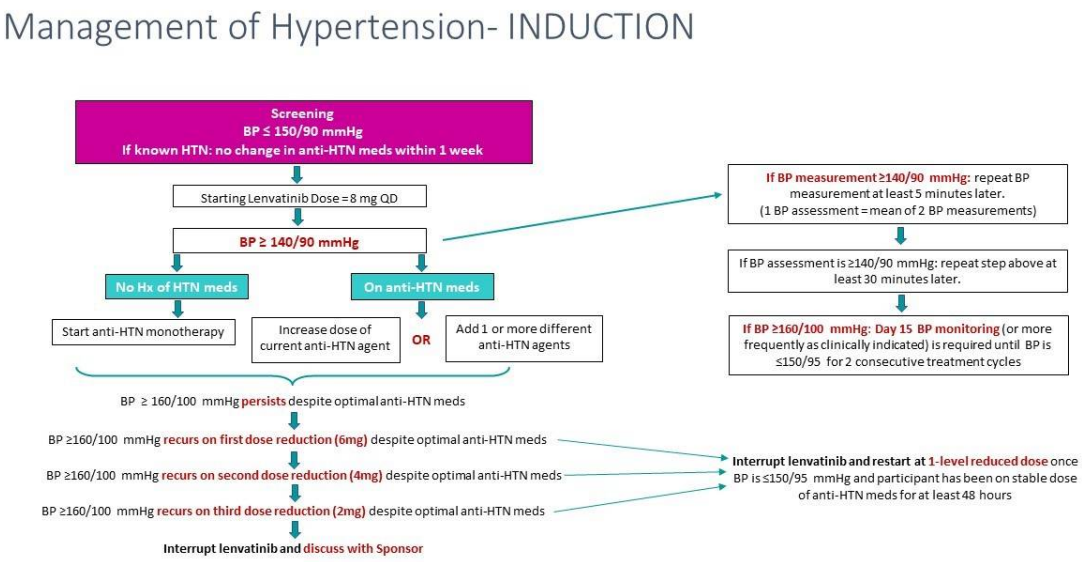
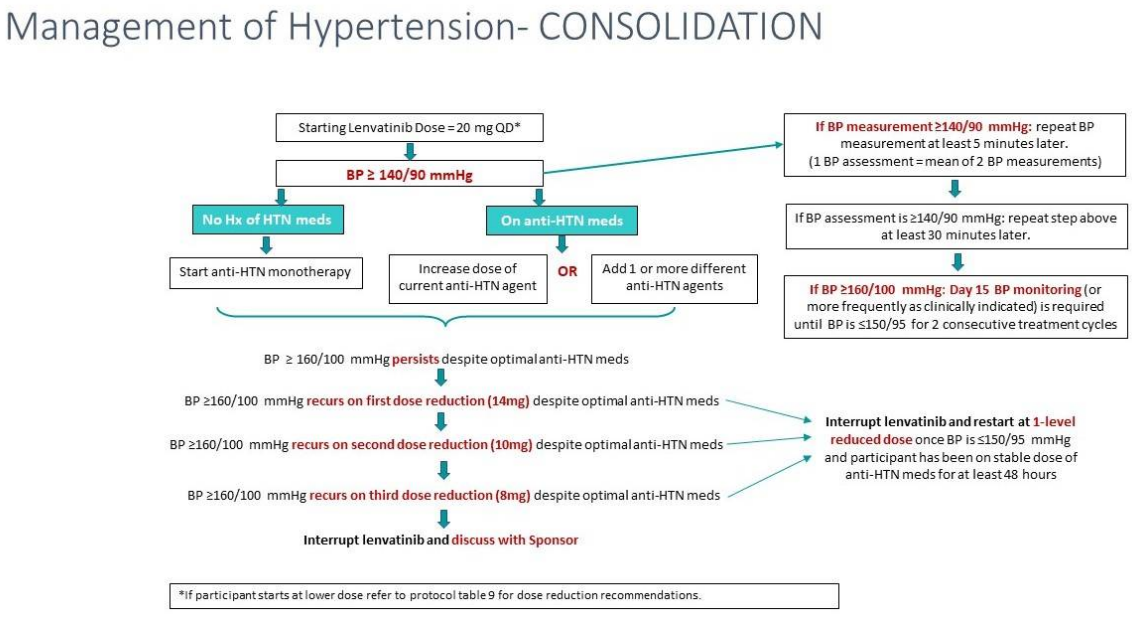


Figure 9 Management of Hypertension – CONSOLIDATION



10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
5-FU	fluorouracil
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
ApaT	All-Participants-as-Treated
ASCO	American Society of Clinical Oncology
ASCP	American Society of Clinical Pathology
AST	aspartate aminotransferase
AUC	area under the curve
BICR	blinded independent central review
bid	twice daily
BMI	body mass index
BP	blood pressure
CAP	College of American Pathologists
CAPOX	capecitabine and oxaliplatin
C_{avg}	average concentration over the dosing interval
CBC	complete blood count
CD28	cluster of differentiation 28
CD3ζ	cluster of differentiation zeta
CHF	congestive heart failure
CI	confidence interval
C_{min}	minimum concentration
C_{max}	maximum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPS	combined positive score

Abbreviation	Expanded Term
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CSAE	clinically significant adverse event
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE v5.0	Common Terminology Criteria for Adverse Events, v5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
DTC	differentiated thyroid cancer
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	executive oversight committee
EORTC QLQ-C30	European Organization For Research & Treatment of Cancer Quality-of-Life Questionnaire Global Health Status

Abbreviation	Expanded Term
EORTC QLQ-STO22	European Organization For Research & Treatment of Cancer Quality-of-Life Questionnaire (Symptom Score For St022)
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQoL 5 Dimension Questionnaire
ER	exposure response
ESMO	European Society for Medical Oncology
EU CTR	European Union Clinical Trial Regulation
FA	final analysis
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FSH	follicle-stimulating hormone
FU	fluorouracil
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GEJ	gastroesophageal junction
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HER-2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality-of-life
HRT	hormone replacement therapy
HUVEC	human umbilical vein endothelial cell
IA	interim analysis
IB	Investigator's Brochure

Abbreviation	Expanded Term
IC_{50}	inhibitor concentration required for 50 percent inhibition
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
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
JRCT	Japan Registry of Clinical Trials
LAM	lactational amenorrhoea method
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
M&N	Miettinen and Nurminen
M&S	modeling and simulation
MAPK	mitogen activated protein kinase
mFOLFOX6	5-FU + oxaliplatin + leucovorin
MHC1	major histocompatibility complex 1
MRI	magnetic resonance imaging
mRNA	messenger RNA

Abbreviation	Expanded Term
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
OME	other medical event
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	disease progression
PD-1	programmed cell death 1
PDGR	platelet derived growth factor
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
Pgp	p-glycoprotein
PI	principal investigator
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PPES	palmar-plantar erythrodysesthesia syndrome
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
q2w	every 2 weeks
q3w	every 3 weeks

Abbreviation	Expanded Term
q6w	every 6 weeks
q12w	every 12 weeks
qd	once daily
QoL	quality-of-life
QTcF	QT interval calculated according to the Fridericia
RAG	receptor for advanced glycation
RCC	renal cell carcinoma
RET	rearranged during transfection
RNA	ribonucleic acid
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SLAB	supplemental lab tests (CRF)
SoA	schedule of assessments
SOC	standard of care
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TAM	tumor-associated macrophage
TB	tuberculosis
TBL	total bilirubin level
TCR	T-cell receptor
TKI	tyrosine kinase inhibitor
TRAE	treatment-related adverse events
ULN	upper limit of normal
UPC	urine protein creatinine
UPCR	urine protein creatinine ratio
US	United States
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell

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

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