Official Protocol Title:	A Phase 3 Randomized Study of Lenvatinib in Combination with Pembrolizumab Versus Standard of Care in Participants with Metastatic Colorectal Cancer Who Have Received and Progressed On or After or Became Intolerant to Prior Treatment
NCT number:	NCT04776148
Document Date:	14 July 2022

Title Page

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Protocol Title: A Phase 3 Randomized Study of Lenvatinib in Combination with Pembrolizumab Versus Standard of Care in Participants with Metastatic Colorectal Cancer Who Have Received and Progressed On or After or Became Intolerant to Prior Treatment

Protocol Number: MK-7902-017-03 (E7080-G000-325)

Compound Number: MK-7902 (E7080/lenvatinib) and MK-3475 (pembrolizumab)

Sponsor Name:

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

The study is part of a collaboration between MSD and Eisai

Legal Registered Address:

126 East Lincoln Avenue

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Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	140284
EudraCT	2020-004289-20

Approval Date: 14 July 2022

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 03	14-JUL-2022	To clarify metastatic liver subgroup language.
Amendment 02	13-APR-2021	Response to Health Authority requests, updating lenvatinib toxicity information.
Amendment 01	12-FEB-2021	Update per country Health Authorities and clarify information.
Original Protocol	16-NOV-2020	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

To clarify metastatic liver subgroup language.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
9.10 Subgroup Analyses	Clarified liver metastasis subgroup language. Removed reference to HRD.	Clarification of parameters. HRD status is not routinely tested in participants with CRC.
Title Page 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
1.3.1 Arm A: Lenvatinib Plus Pembrolizumab Treatment 1.3.2 Arm B: Regorafenib Treatment 1.3.3 Arm B: TAS-102 Treatment	Removed reference to AE/SAE safety assessment on clinic day every 2 weeks.	Text added in error.

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design 4.2.1.3.2 EuroQoL EQ-5D-5L 8.1.1.1 General Informed Consent 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 10.1.2 Financial Disclosure 10.1.3 Data Protection 10.3.5 Recording of AE and SAE 10.7.1 Germany-specific Requirements	Change “he/she” to “the investigator,” or “they” and “his/her” to “their”.	Adopt gender neutral language.
4.4 Beginning and End of Study Definition	Added language for European Economic Area countries	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council
5.1 Inclusion Criteria	#12 Updated language related to breastfeeding and contraception use. #13 Changed to documented informed consent	Clarification of breastfeeding and contraception requirements. Per COVID-19 requirements

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	#9 Removed pacemaker language. #20 Added COVID-19 reference.	To ensure that participants with QTcF interval to >480 ms are not entered into the trial. Adherence to COVID-19 requirements.
6.1 Study Intervention(s) Administered	Updated Table 6 to reflect proper nomenclature for study interventions.	To align with EU CTR.
6.5.1.1 Arm A Prohibited Concomitant Medication(s)	Added COVID-19 information.	Adherence to COVID-19 requirements.
8.3.6 Pregnancy Test	Removed reference to local regulations.	Clarification of information.
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events 10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added language related to investigator documenting SAE related to medication error, misuse, abuse, and their definition. Added new Section 10.3.1.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council.
8.4.7 Events of Clinical Interest 10.3.2 Definition of AE	Added information regarding lenvatinib overdose.	To clarify that lenvatinib overdose without an associated AE is not to be reported as an ECI.
3 Hypotheses, Objectives, and Endpoints 4.2.1.1 Efficacy Endpoints 9.4.3 PRO Endpoints	Changed reference from health utility score / status to VAS.	Clarification of endpoint measure.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	Removed bicarbonate from footnote a in Table 18.	Clarification of testing.
10.7.3 China-specific Requirements	Updated laboratory specimen collection information.	To accommodate central testing timelines for lipase, amylase, and 24-hour urine collection in China. Only applicable for sites that cannot perform these tests locally.
10.7.4 Korea-specific Requirements	Updated hepatic function test collection information.	To align with local regorafenib label.
Throughout Document	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 of Lenvatinib in Combination with Pembrolizumab Versus Standard of Care in Participants with Metastatic Colorectal Cancer Who Have Received and Progressed On or After or Became Intolerant to Prior Treatment

Short Title: A Phase 3 Study of Lenvatinib Plus Pembrolizumab in Previously Treated Participants with Metastatic Colorectal Cancer

Acronym: LEAP-017

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Throughout this protocol, the term RECIST 1.1 refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

In male and female participants with unresectable mCRC that is not MSI-H/dMMR who have received and progressed through or have become intolerant to prior treatment (refer to Section 5.1):

Primary Objectives	Primary Endpoints
Objective: To compare lenvatinib plus pembrolizumab combination therapy to SOC with respect to OS. - Hypothesis (H1): lenvatinib plus pembrolizumab is superior to SOC with respect to OS.	OS: the time from randomization to death due to any cause.
Secondary Objectives	Secondary Endpoints
Objective: To compare lenvatinib plus pembrolizumab combination therapy to SOC with respect to PFS per RECIST 1.1 as assessed by BICR. - Hypothesis (H2): lenvatinib plus pembrolizumab combination therapy is superior to SOC with respect to PFS per RECIST 1.1 by BICR.	PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

Objective: To compare lenvatinib plus pembrolizumab combination therapy to SOC with respect to ORR per RECIST 1.1 as assessed by BICR. - Hypothesis (H3): lenvatinib plus pembrolizumab is superior to SOC with respect to ORR per RECIST 1.1 by BICR.	Objective Response: CR or PR.
Objective: To assess the efficacy of lenvatinib plus pembrolizumab combination therapy and SOC with respect to DOR per RECIST 1.1 by BICR.	DOR, defined as the time from the first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first, in participants demonstrating CR or PR.
Objective: To evaluate the safety and tolerability of pembrolizumab plus lenvatinib versus SOC.	- AEs. - Study intervention discontinuation due to AEs.
Objective: To compare the change from baseline in global health status/QoL, physical functioning, appetite loss and bloating for the combination of pembrolizumab plus lenvatinib to SOC.	Score for the following PROs scales/items: global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).
Objective: To compare the TTD in global health status/QoL, physical functioning, appetite loss and bloating for the combination of pembrolizumab plus lenvatinib to SOC.	TTD, defined as the time from baseline to the first onset of a $\geq$10-point deterioration from baseline in global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Colorectal Carcinoma
Population	Male and female participants with unresectable mCRC that is not MSI-H/dMMR who have received and progressed through or have become intolerant to prior treatment (refer to Section 5.1)
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 40 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 434 participants will be randomized in this study. After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants from China have been enrolled to meet local regulatory requirements.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A	Pembrolizumab	400 mg	Q6W	IV Infusion	Up to 18 administrations (approximately 2 years)	Test Product
	Lenvatinib	20 mg	QD	po	Until progressive disease	Test Product
Arm B	Regorafenib	160 mg[a]	Q4W (QD on Days 1-21, no dose Days 22-28)	po	Until progressive disease	Comparator
	TAS-102[b]	35 mg/m^2	Q4W (BID on Days 1-5 and Days 8-12, no dose on Days 6-7 and on Days 13-28)	po		

Abbreviations: BID=twice daily; IV = intravenously; po = orally; Q6W = every 6 weeks; Q4W = every 4 weeks; QD = daily; Exp=Experimental

a. According to local/institutional guidelines, regorafenib may be administered as follows in Cycle 1: 80 mg regorafenib QD on Cycle 1 Days 1 to 7, then 120 mg QD on Days 8 to 14, followed by 160 mg QD on Days 15 to 21, and 160 mg QD on subsequent cycles (Days 1 to 21).
b. TAS-102 is a combination of trifluridine and tipiracil hydrochloride.

Total Number of Intervention Groups/ Arms	2 intervention groups

Duration of Participation	Each participant will take part in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants may continue treatment with lenvatinib beyond 2 years until progression if they experience clinical benefit as assessed by the investigator, with Sponsor consultation and approval. Participants in Arm A will be permitted to continue study intervention beyond RECIST 1.1 defined disease progression as long as the investigator considers that the participant may experience clinical benefit with continued treatment, and the participant is tolerating study intervention. Imaging should continue to be performed and submitted to the iCRO when progression is identified by the investigator until disease progression is verified by BICR, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All decisions to continue treatment beyond 2 consecutive scans (at least 4 weeks apart) showing progression must be approved by the Sponsor. At the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy. Participants who complete or discontinue study intervention in the absence of radiographic disease progression will have posttreatment follow up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

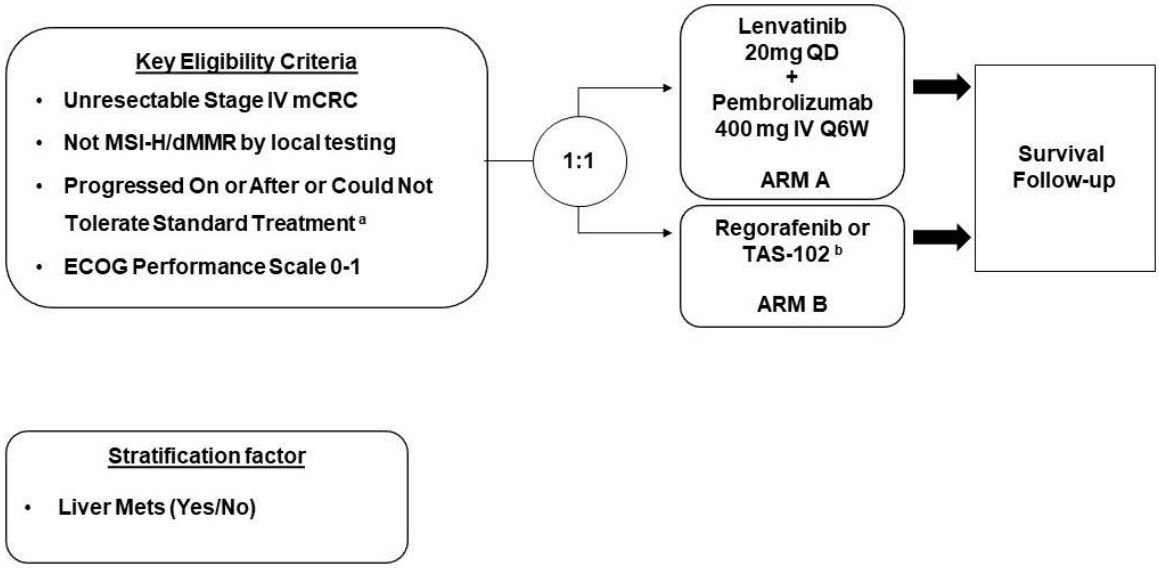
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



a. Refer to Section 5.1, Inclusion Criterion #2 for a list of standard treatments a participant must have received.

b. Refer to Section 1.1 table for Intervention Groups for schedule of administration of regorafenib and TAS-102.

1.3 Schedule of Activities

1.3.1 Arm A: Lenvatinib Plus Pembrolizumab Treatment

Refer to Appendix 7 for country-specific requirements.

Table 1 Arm A: Lenvatinib Plus Pembrolizumab Treatment

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**																**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Administrative Procedures																					
Informed Consent	X																				If the investigator plans to treat beyond disease progression, additional consent is required.
Inclusion/ Exclusion Criteria	X																				
Participant Identification Card	X	X																			Identification card will be updated with randomization number at C1D1.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Demographic and Medical History and family history of premature CV disease	X																				History of Lynch Syndrome needs to be recorded if known
CRC History	X																				Including (but not limited to) staging at the initial diagnosis and at study entry
Prior CRC Therapy Review	X																				Including neo-adjuvant therapy, adjuvant therapy, any chemotherapy, surgery and radiation therapy.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Prior/ Concomitant Medication Review	←															→					Concomitant medications received within 28days before the first dose of study intervention through 30 days after the last dose (or 90 days if used to treat an SAE) will be recorded.
Subsequent Anti-Neoplastic Treatment																	X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinical visit is not feasible, follow up information may be obtained by other means such as telephone or email

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Treatment Eligibility Assessment	X																				Prior to randomization, the investigator must provide rationale for participants to receive regorafenib or TAS-102.
Randomization via IRT		X																			It is strongly preferred that participants receive first dose of study intervention on day of randomization.
Disease-specific Biomarker Data Collection	X																				Including MSI/MMR status, BRAF mutation status, RAS mutation status, PD-L1 expression (if available), TMB (if available) and HRD if available

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Survival Status		←														→					After investigator determined disease progression or start of new anticancer treatment. In addition, on Sponsor request, participants may be contacted for survival status at any time during the study.
Study Administration																					
Pembrolizumab administration		X				X			X			X	X	X							Participant dosed every 6 weeks. Starting from Cycle 7: treatment on D1 of C7, C10, C13, C16, C19, C22, C25 and on D15 of C8, C11, C14, C17, C20, C23, C26
Lenvatinib Dispensing		X		X	X	X	X	X	X	X	X	X	X	X	X	X					Dispensed every 2 weeks

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Lenvatinib Container Returned		X		X	X	X	X	X	X	X	X	X	X	X	X	X					Container should be returned every 2 weeks
Lenvatinib Administration po QD		◄———														———►					Taken at home every day (once daily) continuously On pembro-lizumab clinic day will be taken 0-4 hours after pembrolizumab.

Study Period	Screen-ing	Intervention (28-Day Cycles)																Posttreatment Visits			Notes
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Efficacy																					
Tumor Imaging (Chest, abdomen and Pelvis)	X	←————————————————→ (arrow from C1 through Efficacy FU)																			Acquired at Screening; then first on-study imaging assessment after initial tumor imaging at Screening should be performed at 8 weeks (56 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 8 weeks (56 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle.

Study Period	Screen-ing	Intervention (28-Day Cycles)															Posttreatment Visits			Notes
Visit Number/ Title	Screen-ing	C1			C2		C3		C4		C5		C6* to C26		≥C27		EOT	Safety FU	Efficacy FU	Sur-vival FU	
Cycle Day		1	8	15	1	15	1	15	1	15	1	15	1	15	1	15					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	± 3	±3	±3	±3	±3	At DC	Approx 30 days after last dose	Q8W (± 7d)	Q12W (± 14d)	
Patient Reported Outcomes																					
EQ-5D-5L EORTC QLQ-C30 EORTC QLQ-CR-29		X		X	X	X	X	X	X		X		X				X	X			ePROs should be performed in the order in the table. It is strongly recommended that ePROs are completed prior to drug administration, adverse event evaluation and disease status notification. ePRO collection is required at D1 and D15 of C1 through C3 and then D1 of C4 through C12 and then D1 of every other cycle thereafter (ie, C14, C16, etc. up to C26) until end of treatment visit or treatment discontinuation, or 2 years, whichever occurs first, and at the D30 posttreatment safety follow-up visit.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Safety Assessments																					
Full Physical Examination including height	X																X				To be performed within 7 days prior to start of study treatment.
Directed Physical Examination		X		X	X	X	X	X[#]	X		X	X[#]	X	X[#]	X	X[#]		X				On C1D1, C1D15, C2D1, C2D15 and on D1 of each cycle and Safety visit. In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during the study, as clinically indicated. [#]Additional testing on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15, etc)

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Weight	X	X			X		X		X		X		X		X		X	X			Taken every 4 weeks, EOT and Safety Visit.
Vital Signs (BP, pulse, RR, temp) and height	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			To be performed within 7 days prior to start of study treatment and every 2 weeks, EOT and Safety Visit; BP and pulse will be measured after the participant has been resting for 5 minutes. Height measured at screening only.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
12-lead ECG	X	X			X						X		X		X		X	X			ECG at screening, C1D1, C2D1, D1 of every third cycle (12 weeks) thereafter (eg, C5, C8, C11, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants (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.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
MUGA Scan or ECHO	X																	X			Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study. Additional LVEF assessments may be performed as clinically Indicated.
ECOG Performance Status	X*	X			X		X		X		X		X		X		X	X			*At screening and within 3 days before initiation of study intervention To be obtained every 4 weeks on D1 of every cycle, EOT and Safety visit.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
AE/SAE Monitoring	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→			AEs monitored up to 30 days after last dose. SAEs monitored up to 90 days. Pregnancy monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Telephone Contact Visit			X																		Telephone contact or visit on C1D8 will assess participants for development of early toxicity and to assess blood pressure. Refer to Section 8.11.2.1 for further details. An unscheduled visit can occur prior C1D15 to next clinic visit if necessary, for safety.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Laboratory Procedures																					
Hematology and Chemistry	X*	X		X	X		X	X#	X		X	X#	X	X#	X	X#	X	X			*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. Predose on C1D15 and on D1 of every cycle (C2D1, C3D1, C4D1 etc.), EOT and Safety visit. #Additional testing predose on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15, etc)

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Urine Dipstick[a]	X*			X		X	X	X[#]	X		X	X[#]	X	X[#]	X	X[#]	X	X			[*]Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. If urine dipstick is not able to be performed, urinalysis is acceptable.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Thyroid function (T3, T4, and TSH)	X*	X			X		X		X		X		X		X		X	X			*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. Free T3 and T4 are acceptable. Collect on D1 of each cycle (every 4 weeks), EOT and Safety visit.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
INR or PT and aPTT (baseline only)	X*																				*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. Additional testing is to be performed as clinically indicated for participants taking anticoagulants

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Serum Tumor Marker (CEA and CA-19-9)	X	X					X				X		X		X		X				Can be obtained within 72 hours prior to dosing at cycle start. Screening, D1 of every other cycle (C1, C3, C5, C7 etc.), EOT.
Serum hCG or Urine Pregnancy Test (WOCBP only)	X				X		X		X		X		X		X		X	X			WOCBP require a negative test prior to randomization. If more than 24 hours have elapsed prior to the first dose of study intervention, another pregnancy test is required. Testing must be conducted as clinically indicated. Serum test is only required if urine test is positive or not evaluable.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Serum FSH (WONCBP only)	X																				In the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in postmenopausal range is required.
HIV, HBsAg, HCV	X																				Only if required by local health authority.
Biomarker Assessments																					
Blood for Serum Biomarker Analysis		X				X			X								X				Collect predose on C1D1, C2D15, C4D1 and at EOT.
Blood for RNA Analysis		X				X			X								X				Collect predose on C1D1, C2D15, C4D1 and at EOT.

Study Period	**Screen-ing**	**Intervention (28-Day Cycles)**															**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screen-ing**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6* to C26**		**≥C27**		**EOT**	**Safety FU**	**Efficacy FU**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Blood for ctDNA Analysis		X				X			X		X		X		X		X				Collect predose on C1D1, C2D15, C4D1 and then collected on Day 1 of every other cycle (C5D1, C7D1, C9D1, etc.) and at EOT.
Blood for Genetic Analysis		X																			Collect predose.
Archival or Newly Obtained Tissue Collection	X																				Archival tissue should be ≤5 years. If obtained at Screening, the procedure should be performed before screening /baseline scans are performed. Detailed instructions for the tissue specimen collection process and shipment are provided in the Laboratory Manual.

Study Period	Screen-ing	Intervention (28-Day Cycles)															Posttreatment Visits			Notes
Visit Number/ Title	Screen-ing	C1			C2		C3		C4		C5		C6* to C26		≥C27		EOT	Safety FU	Efficacy FU	Sur-vival FU	
Cycle Day		1	8	15	1	15	1	15	1	15	1	15	1	15	1	15					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	± 3	±3	±3	±3	±3	At DC	Approx 30 days after last dose	Q8W (± 7d)	Q12W (± 14d)	

a. For urine dipstick, perform 3 days prior to the first dose. Collect at screening, after C1, collect samples predose at C1D15, C2D15, and up to 3 days before D1 of each cycle, EOT and Safety Follow-up. Additional testing should be performed predose on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15, etc). Participants with ≥2+ proteinuria on urine dipstick during screening will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24-hour will not be eligible. See Section 6.6.2.2 for management of proteinuria. After lenvatinib is discontinued, urine dipstick testing no longer required.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BICR = blinded independent central review; BP = blood pressure; hCG; = human chorionic gonadotropin; C = cycle; CEA = carcinoembryonic antigen; ctDNA = circulating tumor DNA; D = day; ePRO = electronic patient-reported outcome; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; EQ-5D-5L = European Quality of Life Five-Dimensional Five-Level Scale Questionnaire; FSH = follicle-stimulating hormone; FU = follow-up; HBsAg = hepatitis B virus surface virus antigen; HIV = human immunodeficiency virus; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MMRd = mismatch repair deficiency; MMRp = mismatch repair protein; MMS = microsatellite Stable; MSI-H = microsatellite instability-high; MUGA = multigated acquisition; PRO = patient-reported outcome; PT = prothrombin time; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QLQ-C30 = Quality of Life Questionnaire Core 30 items; QTcF = QT interval corrected with Fridericia's formula; RNA= ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SoA = schedule of activities; T3 = triiodothyronine; T4 = thyroxine; TEA = Treatment Eligibility Assessment; TMB = Tumor mutational burden; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of nonchildbearing potential.

1.3.2 Arm B: Regorafenib Treatment

Refer to Appendix 7 for country-specific requirements.

Table 2 Arm B: Regorafenib Treatment

Study Period	**Screening**	**Intervention (28-Day Cycles)**														**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Administrative Procedures																			
Informed Consent	X																		
Inclusion/ Exclusion Criteria	X																		
Participant Identification Card	X	X																	Identification card will be updated with randomization number at C1D1.
Demo-graphics and Medical History and family history of premature CV disease	X																		History of Lynch Syndrome needs to be recorded if known

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Colorectal Cancer History	X																		Including (but not limited to) staging at the initial diagnosis and at study entry
Prior CRC Therapy Review	X																		Including neo-adjuvant therapy, adjuvant therapy, any chemotherapy, surgery and radiation therapy.
Prior/ Conco-mitant Medication Review	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→				Concomitant medications received within 30 days before the first dose of study intervention through 30 days after the last dose (or 90 days if used to treat an SAE) will be recorded.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Subsequent Anti-neoplastic Treatment															X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinical visit is not feasible, follow up information may be obtained by other means such as telephone or email
Treatment Eligibility Assessment	X																		Prior to randomization, the investigator must provide rationale for participants to receive regorafenib or TAS-102.
Allocation (Rando-mization) via IRT		X																	It is strongly preferred that participants receive first dose of study intervention on day of randomization.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Disease-specific Biomarker Data Collection	X																		Including MSI/MMR status, BRAF mutation status, RAS mutation status, PD-L1 expression (if available), TMB (if available) and HRD if available
Survival Status		◄																►	After investigator determined disease progression or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Study Administration																			
Regora-fenib Adminis-tration		←												→					Q4W Regorafenib: QD Days 1-21, no dose Days 22-28. The C1D1 dose must be given to the participant at the site.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Efficacy																			
Tumor Imaging (Chest, Abdomen, and Pelvis)	X	←	—	—	—	—	—	—	—	—	—	—	—	→					Acquired at Screening; then first on-study imaging assessment after initial tumor imaging at Screening should be performed at 8 weeks (56 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 8 weeks (56 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle.

Study Period	Screening	Intervention (28-Day Cycles)													Posttreatment Visits			Notes
Visit Number/ Title	Screening	C1			C2		C3		C4		C5		C6 to C26		EOT	Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	15	1	15	1	15	1	15	1	15					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At DC	Approx 30 days after last dose	Q8W (± 7d)	Q12W (± 14d)	
Patient Reported Outcomes																			
EQ-5D-5L EORTC QLQ-C30 EORTC QLQ-CR-29		X		X	X	X	X	X	X		X		X		X	X			ePROs should be done in the order in the table. It is strongly recommended that ePROs are completed prior to drug administration, adverse event evaluation and disease status notification. ePRO collection is required at D1 and D15 of C1 through C3 and then D1 of C4 through C12 and then D1 of every other cycle thereafter (ie, C14, C16, etc. up to C26) and at end of treatment visit or treatment discontinuation, or 2 years, whichever occurs first, and at the D30 posttreatment safety follow-up visit.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Safety Assessments																			
Full Physical Examination including height	X														X				To be performed within 7 days prior to start of study treatment
Directed Physical Examination		X		X	X	X	X	X[#]	X		X	X[#]	X	X[#]		X				On C1D1, C1D15, C2D1, C2D15 and on D1 of each cycle and Safety visit. In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during the study, as clinically indicated. [#]Additional testing on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15, etc)
Weight	X	X			X		X		X		X		X		X	X			Taken every 4 weeks, EOT and Safety Visit

Study Period	**Screening**	**Intervention (28-Day Cycles)**														**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Vital Signs (resting BP, pulse, RR, temp) and height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			To be performed within 7 days prior to start of study treatment and then weekly for the first 6 weeks of treatment and then every 2 weeks, EOT and Safety Visit. BP and pulse will be measured after the participant has been resting for 5 minutes. Height measured at screening only.
12-lead ECG with QTcF Determine-eation	X	X			X						X		X		X	X			ECG at screening, C1D1, C2D1, D1 of every third cycle (12 weeks) thereafter (eg, C5, C8, C11, etc.), EOT, and Safety follow-up visits.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
MUGA Scan or ECHO	X															X			Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study. Additional LVEF assessments may be performed as clinically indicated.
ECOG Performance Status	X*	X			X		X		X		X		X		X	X			*At screening and within 3 days before initiation of study intervention. To be obtained every 4 weeks on D1 of every cycle, EOT and Safety visit.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Telephone Contact Visit			X																Telephone contact or visit on C1D8 will assess participants for development of early toxicity. The investigator or medically qualified designee (consistent with local requirements) will assess participants for development of early toxicity. An unscheduled visit can occur prior C1D15 to next clinic visit if necessary, for safety.

Study Period	**Screening**	**Intervention (28-Day Cycles)**														**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
AE/SAE monitoring	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→			AEs monitored up to 30 days after last dose. SAEs monitored up to 90 days. Pregnancy monitored up to 180 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.

Study Period	**Screening**	**Intervention (28-Day Cycles)**														**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Local Laboratory Procedures																			
Hema-tology and Chemistry	X*	X		X	X	X	X	X[#]	X		X	X[#]	X	X[#]	X	X			*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. Predose on C1D15 and on D1 of every cycle (C2D1, C3D1, C4D1 etc.), EOT and Safety visit. [#]Additional testing predose on C2D15 and on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15, etc)

Study Period	Screening	Intervention (28-Day Cycles)													Posttreatment Visits			Notes
Visit Number/ Title	Screening	C1			C2		C3		C4		C5		C6 to C26		EOT	Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	15	1	15	1	15	1	15	1	15					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At DC	Approx 30 days after last dose	Q8W (± 7d)	Q12W (± 14d)	
Urine Dipstick[a]	X*			X		X	X	X	X		X	X[#]	X	X	X	X			[*]Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. If urine dipstick is unable to be performed, urinalysis is acceptable.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Thyroid function (T3, T4, and TSH)	X*	X			X		X		X		X		X		X	X			*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. Free T3 and T4 are acceptable. Collect on D1 of each cycle (every 4 weeks), EOT and Safety visit

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
INR or PT and aPTT (baseline only)	X*																		*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. Additional testing is to be performed as clinically indicated for participants taking anticoagulants.
Serum Tumor Marker (CEA and CA-19-9)	X	X					X				X		X		X				Can be obtained within 72 hours prior to dosing at cycle start. Screening, D1 of every other cycle (C1, C3, C5, C7 etc.), EOT.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Serum hCG or Urine Pregnancy Test (WOCBP only)	X				X		X		X		X		X		X	X			WOCBP require a negative test prior to randomization. If more than 24 hours have elapsed prior to the first dose of study intervention, another pregnancy test is required. Testing must be conducted as clinically indicated. Serum test is only required if urine test is positive or not evaluable.
Serum FSH (WONCBP only)	X																		In the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in postmenopausal range is required.
HIV, HBsAg, HCV	X																		Testing is not required unless mandated by local health authority.

Study Period	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title	**Screening**	**C1**			**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Biomarker Assessments																			
Blood for Serum Biomarker Analysis		X				X			X						X				Collect predose on C1D1, C2D15, C4D1 and at EOT.
Blood for RNA Analysis		X				X			X						X				Collect predose on C1D1, C2D15, C4D1 and at EOT.
Blood for ctDNA Analysis		X				X			X		X		X		X				Collect at predose on C1D1, C2D15, C4D1, and then collected on Day 1 of every other cycle (C5D1, C7D1, C9D1, etc.) and at EOT.
Blood for Genetic Analysis		X																	Collect predose.

Study Period	Screening	Intervention (28-Day Cycles)													Posttreatment Visits			Notes
Visit Number/ Title	Screening	C1			C2		C3		C4		C5		C6 to C26		EOT	Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	15	1	15	1	15	1	15	1	15					
Scheduling Window (days)	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At DC	Approx 30 days after last dose	Q8W (± 7d)	Q12W (± 14d)	
Archival or Newly Obtained Tissue Collection	X																		Archival tissue should be ≤5 years. If obtained at Screening, the procedure should be performed before screening /baseline scans are performed. Detailed instructions for the tissue specimen collection process and shipment are provided in the Laboratory Manual.

a. For urine dipstick, perform 3 days prior to the first dose. Collect at screening, after C1, collect samples predose at C1D15, C2D15, and up to 3 days before D1 of each cycle, EOT and Safety follow-up. #Additional testing should be performed predose on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15, etc) Participants with ≥1+ proteinuria on urine dipstick during screening will undergo 24-hour urine collection for quantitative assessment of proteinuria.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BICR = blinded independent central review; BP = blood pressure; hCG; = human chorionic gonadotropin; C = cycle; CEA = carcinoembryonic antigen; ctDNA = circulating tumor DNA; D = day; ePRO = electronic patient-reported outcome; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; EQ-5D-5L = European Quality of Life Five-Dimensional Five-Level Scale Questionnaire; FSH = follicle-stimulating hormone; FU = follow-up; HBsAg = hepatitis B virus surface virus antigen; HIV = human immunodeficiency virus; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MMRd = mismatch repair deficiency; MMRp = mismatch repair protein; MMS = microsatellite Stable; MSI-H = microsatellite instability-high; MUGA = multigated acquisition; PRO = patient-reported outcome; PT = prothrombin time; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QLQ-C30 = Quality of Life Questionnaire Core 30 items; QTcF = QT interval corrected with Fridericia's formula; RNA= ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SoA = schedule of activities; T3 = triiodothyronine; T4 = thyroxine; TEA = Treatment Eligibility Assessment; TMB = Tumor mutational burden; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of nonchildbearing potential.

1.3.3 Arm B: TAS-102 Treatment

Refer to Appendix 7 for country-specific requirements.

Table 3 Arm B: TAS-102 Treatment

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Administrative Procedures																		
Informed Consent	X																	
Inclusion/ Exclusion Criteria	X																	
Participant Identification Card	X	X																Identification card will be updated with randomization number at C1D1.
Demo-graphics and Medical History [and family history of premature CV disease]	X																	History of Lynch Syndrome needs to be recorded if known

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
CRC History	X																	Including (but not limited to) staging at the initial diagnosis and at study entry
Prior CRC Therapy Review	X																	Neo-adjuvant therapy, adjuvant therapy, any chemotherapy, surgery and radiation therapy during the treatment of the metastatic disease
Prior/ Concomitant Medication Review	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→			Concomitant medications received within 30 days before the first dose of study intervention through 30 days after the last dose (or 90 days if used to treat an SAE) will be recorded.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Subsequent antineoplastic treatment														X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinical visit is not feasible, follow up information may be obtained by other means such as telephone or email
Treatment Eligibility Assessment (TEA)	X																	Prior to randomization, the investigator must provide rationale for participants to receive regorafenib or TAS-102.
Allocation/ Randomization via IRT		X																It is strongly preferred that participants receive first dose of study intervention on day of randomization.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Disease-specific Biomarker Data Collection	X																	Including MSI/MMR, BRAF mutation status, RAS mutation status, PD-L1 expression (if available), TMB (if available) and HRD if available
Survival Status		←												→				After investigator determined disease progression or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Study Administration																		
TAS-102		←											→					Q4W TAS-102: BID on Days 1-5 and on Days 8-12, no dose Days 6-7 or Days 13-28. The C1D1 dose must be given to the participant at the site. Participants must return to the site every 2 weeks.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Efficacy																		
Tumor Imaging (Chest, Abdomen and Pelvis)	X	←											→					Acquired at Screening; then first on-study imaging assessment after initial tumor imaging at Screening should be performed at 8 weeks (56 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 8 weeks (56 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Patient Reported Outcomes (PRO)																		
EQ-5D-5L EORTC QLQ-C30 EORTC QLQ-CR-29		X	X	X	X	X	X	X		X		X		X	X			ePROs should be done in the order in the table. It is strongly recommended that ePROs are completed prior to drug administration, adverse event evaluation and disease status notification. ePRO collection is required at D1 and D15 of C1 through C3 and then D1 of C4 through C12 and then D1 of every other cycle thereafter (i.e. C14, C16, etc. up to C26) and at end of treatment visit or treatment discontinuation, or 2 years, whichever occurs first, and at the D30 posttreatment safety follow-up visit.
Safety Assessment																		
Full Physical Examination including height	X													X				To be performed within 7 days prior to start of study treatment.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Directed Physical Examination		X	X	X	X	X	X[#]	X		X	X[#]	X	X[#]		X			On C1D1, C1D15, C2D1, C2D15 and on D1 of each cycle and Safety visit. In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during the study, as clinically indicated. [#]Additional testing on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15 etc)
Weight	X	X		X		X		X		X		X		X	X			Taken every 4 weeks, EOT and Safety Visit. TAS-102 dose must be adjusted if weight fluctuates by ≥10%.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Vital Signs (resting BP, pulse, RR, temp) and height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			To be performed within 7 days prior to start of study treatment and every 2 weeks, EOT and Safety Visit; BP and pulse will be measured after the participant has been resting for 5 minutes. Height measured at screening only.
12-lead ECG with QTcF Determination	X	X		X						X		X		X	X			ECG at screening, C1D1, C2D1, D1 of every third cycle (12 weeks) thereafter (eg, C5, C8, C11, etc.), EOT, and Safety follow-up visits

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
MUGA Scan or ECHO	X														X			Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study. Additional LVEF assessments may be performed as clinically indicated.
ECOG Performance Status	X*	X		X		X		X		X		X		X	X			*At screening and within 3 days before initiation of study intervention. To be obtained every 4 weeks on D1 of every cycle, EOT and Safety visit.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
AE/SAE monitoring	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→			AEs monitored up to 30 days after last dose. SAEs monitored up to 90 days. Pregnancy monitored up to 180 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Laboratory Procedures																		
Hematology and Chemistry	X*	X	X	X		X	X#	X		X	X#	X	X#	X	X			*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. Predose on C1D15 and on D1 of every cycle (C2D1, C3D1, C4D1 etc.), EOT and Safety visit. #Additional testing predose on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15, etc)

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Urine Dipstick[a]	X*		X		X	X	X	X		X	X[#]	X	X	X	X			*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. If urine dipstick is unable to be performed, urinalysis is acceptable.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Thyroid function (T3, T4, and TSH)	X*	X		X		X		X		X		X		X	X			*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. Free T3 and T4 are acceptable. Collect on D1 of each cycle (every 4 weeks), EOT and Safety visit

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
INR or PT and aPTT (baseline only)	X*																	*Screening laboratory assessments MUST be done within 3 days of first dose or on C1D1 if results are available before randomization and dosing. After C1, predose laboratory procedures can be conducted up to 72 hours before dosing. **Additional testing is to be performed as clinically indicated for participants taking anticoagulants.**
Serum Tumor Marker (CEA and CA-19-9)	X	X				X				X		X		X				Can be obtained within 72 hours prior to dosing at cycle start; Screening, D1 of every other cycle (C1, C3, C5, C7 etc.), EOT.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Serum hCG or Urine Pregnancy Test (WOCBP only)	X			X		X		X		X		X		X	X			WOCBP require a negative test prior to randomization. If more than 24 hours have elapsed prior to the first dose of study intervention, another pregnancy test is required. Testing must be conducted as clinically indicated. Serum test is only required if urine test is positive or not evaluable.
Serum FSH (WONCBP only)	X																	In the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in postmenopausal range is required.
HIV, HBsAg, HCV	X																	Testing is not required unless mandated by local health authority.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Central Laboratory Assessments																		
Blood for Serum Biomarker Analysis		X			X			X						X				Collect predose on C1D1, C2D15, C4D1 and at EOT.
Blood for RNA Analysis		X			X			X						X				Collect predose on C1D1, C2D15, C4D1, and at EOT.
Blood for ctDNA Analysis		X			X			X		X		X		X				Collect at predose on C1D1, C2D15, C4D1, and then collected on Day 1 of every other cycle (C5D1, C7D1, C9D1, etc.) and at EOT.
Blood for Genetic Analysis		X																Collect predose.

Study Period:	**Screening**	**Intervention (28-Day Cycles)**													**Posttreatment Visits**			**Notes**
Visit Number/ Title:	**Screening**	**C1**		**C2**		**C3**		**C4**		**C5**		**C6 to C26**		**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**					
Scheduling Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**Approx 30 days after last dose**	**Q8W (± 7d)**	**Q12W (± 14d)**	
Archival or Newly Obtained Tissue Collection	X																	Archival tissue should be ≤5 years. If obtained at Screening, the procedure should be performed before screening /baseline scans are performed. Detailed instructions for the tissue specimen collection process and shipment are provided in the Laboratory Manual.

a. For urine dipstick, perform 3 days prior to the first dose. Collect at screening, after C1, collect samples predose at C1D15, C2D15, and up to 3 days before D1 of each cycle, EOT and Safety follow-up. #Additional testing should be performed predose on D15 every 8 weeks starting from C3 (C3D15, C5D15, C7D15, C9D15, etc) Participants with ≥1+ proteinuria on urine dipstick during screening will undergo 24-hour urine collection for quantitative assessment of proteinuria.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BICR = BP = blood pressure; hCG; = human chorionic gonadotropin; C = cycle; CEA = carcinoembryonic antigen; ctDNA = circulating tumor DNA; D = day; ePRO = electronic patient-reported outcome; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; EQ-5D-5L = European Quality of Life Five-Dimensional Five-Level Scale Questionnaire; FSH = follicle-stimulating hormone; FU = follow-up; HBsAg = hepatitis B virus surface virus antigen; HIV = human immunodeficiency virus; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MMRd = mismatch repair deficiency; MMRp = mismatch repair protein; MMS = microsatellite Stable; MSI-H = microsatellite instability-high; MUGA = multigated acquisition; PRO = patient-reported outcome; PT = prothrombin time; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QLQ-C30 = Quality of Life Questionnaire Core 30 items; QTcF = QT interval corrected with Fridericia's formula; RNA= ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SoA = schedule of activities; T3 = triiodothyronine; T4 = thyroxine; TEA = Treatment Eligibility Assessment; TMB = Tumor mutational burden; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of nonchildbearing potential.

2 INTRODUCTION

This study is a Phase 3 randomized, controlled, open-label, multi-center study evaluating the safety and efficacy of lenvatinib plus pembrolizumab in comparison to SOC in participants with mCRC who progressed on or could not tolerate prior treatment before participating in the study, as defined in Section 5.1.

2.1 Study Rationale

Colorectal cancer is a serious, life-threatening condition. Worldwide, CRC is the second leading cause of cancer-related death with ~881,000 cancer-related deaths and a global incidence of ~1.8M (~10% of all cancers) in 2018 [Bray, F., et al 2018]. In the US, CRC is the third most common diagnosed cancer [Siegel, R. L., et al 2020]. It is estimated that 147,950 individuals will be newly diagnosed with CRC and 53,200 CRC deaths will occur in 2020 [Siegel, R. L., et al 2020]. The annual age-adjusted incidence rate is 38.2 per 100,000 persons and the mortality rate is 13.9 per 100,000 persons [Siegel, R. L., et al 2020] [National Cancer Institute 2020]. The median age at diagnosis is 67 years [National Cancer Institute 2020]. Stage at diagnosis is the most important predictor of survival. The 5-year relative survival rate for CRC was approximately 64% with only 14% for distant disease (22% of CRC patients at diagnosis) [National Cancer Institute 2020].

Despite improvements in treatment and earlier detection through screening, prognosis remains poor for patients with recurrent or distant disease; therefore, mCRC continues to be a serious, life-threatening condition.

Across all stages of disease, 95% of mCRC patients have tumors that are not MSI-H/dMMR. Despite recent advances, treatment for most mCRC patients is palliative with few patients achieving long-term survival. Primary treatment with two-drug combinations of fluorouracil (plus leucovorin) and either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) plus bevacizumab are widely adopted treatments for metastatic colorectal cancer (NCCN; ESMO; JSCCR guidelines). Initial treatment strategies led to similar results regardless of which drug — irinotecan or oxaliplatin — was used; therefore, the choice of the primary treatment regimen is commonly based on the physician's or patient's preferences, regional differences, and whether the patient has or has not already received an adjuvant oxaliplatin-containing treatment.

Treatment options for heavily pretreated patients beyond the second-line setting are limited and associated toxicities can be severe. Although regorafenib and TAS-102 are the 2 commonly accepted SOC therapies for patients who have been treated with fluoropyrimidine-, irinotecan-, oxaliplatin-containing chemotherapies, anti-VEGF and an anti-EGFR agent (if RAS [KRAS/NRAS] WT), they offer minimal benefit with an ORR of ≤2% for both agents. In the CORRECT study, a median PFS and OS reported among patients randomized to the regorafenib arm was 2 months (95% CI: 1.9-2.3) and 6.4 months (95% CI 5.8-7.3), respectively [Grothey, A., et al 2013]. In the RECOURSE study, the median PFS and OS reported among patients randomized to the TAS-102 arm was 2 months (95% CI: 1.9-2.1) and 7.1 months (95% CI 6.5-7.8), respectively [Mayer, R. J., et al 2015].

Several distinct genetically defined subgroups of patients with mCRC will also be allowed to participate in LEAP-017. Although new therapies are becoming available for these patients in addition to SOC, their prognosis remains dismal. Therefore, lenvatinib in combination with pembrolizumab will also be evaluated in these subgroups of patients.

Patients with *RAS* WT mCRC represent about 52% of the patient population with mCRC. The current SOC for patients with RAS WT mCRC is FOLFOX or FOLFIRI in combination with cetuximab or panitumumab in the first-line setting [Stintzing, S., et al 2017] [Stintzing, S., et al 2016]; FOLFIRI plus panitumumab in the second-line setting; and panitumumab monotherapy following disease progression after prior chemotherapy treatment (fluoropyrimidine-, oxaliplatin- and irinotecan-containing regimens). The activity of panitumumab monotherapy in 3L has been compared to that of cetuximab, the first approved anti-EGFR agent, in an open-label randomized Phase 3 trial in patients with chemotherapy-refractory KRAS exon 2 WT mCRC[Price, T. J., et al 2014]. Panitumumab was noninferior to cetuximab in terms of OS, PFS, and ORR, with reported OS of 10.4 months and 10 months, respectively (HR 0.97, 95% CI 0.84–1.11, p=0.0007). Thus, patients with *RAS* WT have a high unmet need in that setting.

The *BRAF* V600E mutation occurs in approximately 10% of patients with metastatic colorectal cancer, with recent estimates ranging from as low as 5% to as high as 21% [Clarke, C. N. 2015]. This mutation identifies a distinct subtype of colorectal cancer and patients with metastatic colorectal cancer with the *BRAF* V600E mutation have a poor prognosis, with a median overall survival of 4 to 6 months after failure of initial therapy [Tran, B., et al 2011] [Loupakis, F., et al 2014]. Recently, results from the BEACON randomized Phase 3 study showed that a combination of the BRAF inhibitor encorafenib, in combination with the anti-EGFR monoclonal antibody cetuximab, +/- the MEK inhibitor binimetinib resulted in significantly longer overall survival and a higher response rate than standard therapy in patients with metastatic colorectal cancer with the *BRAF* V600E mutation. Among the 665 patients enrolled and randomized 1:1:1 to either encorafenib, binimetinib, and cetuximab (triplet-therapy group); encorafenib and cetuximab (doublet-therapy group); or the investigators' choice of either cetuximab and irinotecan or cetuximab and FOLFIRI (control group), the median OS was 9.3 months in the triplet-therapy and doublet-therapy groups, and 5.9 months in the control group (HR=0.60 [95%CI: 0.47-0.75] and HR=0.61 [95%CI: 0.48-0.77], respectively). The confirmed response rate was 27% (95% CI, 21 to 33) in the triplet-therapy, 20% (95% CI, 15 to 25) in the doublet-therapy group and 2% (95% CI, <1 to 5) in the control group. AEs of Grade 3 or higher occurred in 58% of patients in the triplet-therapy group, in 50% in the doublet-therapy group, and in 61% in the control group [Kopetz, S., et al 2019] [Kopetz, S., et al 2019].

The doublet combination was approved in the US and encorafenib is indicated in combination with cetuximab for patients with mCRC with a BRAF V600E mutation after prior therapy (refer to current package insert for encorafenib). It is anticipated that doublet combination will be approved and licensed in several countries. In LEAP-017, participants with a BRAF V600E mutation will be eligible if they have received all applicable SOC, including encorafenib in combination with cetuximab (doublet) when locally licensed and available.

Microsatellite instability-high or dMMR CRC comprises approximately 15% of sporadic CRC and 5% of Stage IV CRC, whereas MSS CRC comprises the remainder [Smyrk, T. C., et al 2001] [Xiao, Y. 2015]. The estimates for MSI-H/dMMR CRC in Stage IV patients range from ~3.5% to 5%. Recently, KEYNOTE-177 and KEYNOTE-164 demonstrated that pembrolizumab showed significant efficacy in monotherapy whether in 1L or 2L+ (Section 2.2.2.3). These patients represent a separate subgroup of mCRC patients with a different prognosis due to the availability of anti-PD1 mAbs and will not be included in LEAP-017.

Therefore, patients who received prior treatment for mCRC with tumors that are not MSI-H/pMMR (including *RAS* or BRAF V600E mutated or *RAS* WT tumors) remain a population with a high unmet medical need. Developing novel combinations to improve the clinical outcome in this population is crucial. Emerging data suggest that combining lenvatinib with pembrolizumab may provide improved efficacy in mCRC as well as in other indications.

2.2 Background

Lenvatinib (also known as E7080 or MK-7902) inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including FGF receptors FGFR1, 2, 3, and 4; PDGFRα, KIT, and RET. Lenvatinib exhibits antiproliferative activity in cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGFR substrate 2α phosphorylation.

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.

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

Information on the SOC (regorafenib or TAS-102) in Arm B is provided in Section 2.2.4 and respective approved labeling as per local regulations.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Lenvatinib

Angiogenesis is defined as the formation of new blood vessels from a preexisting vascular network and is essential for tumor growth and metastasis. The VEGF family of receptors (VEGFRs 1 to 3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. 2008] [Tammela, T. 2010] Accumulated evidence suggests that FGF and its receptor

tyrosine kinase, FGFR play important roles for tumor angiogenesis [Cross, M. J. 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), and VEGFR3 (FLT4), FGFR1-4, PDGFRα, 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 inhibits 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 HUVECs 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, 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 exhibited 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.

2.2.1.2 Pembrolizumab

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 upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70,

which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in mCRC.

2.2.1.3 Pembrolizumab Plus Lenvatinib

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 TILs 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+ Tregs correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

In nonclinical 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 anti-human PD-1 humanized mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared to 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 to that of the respective monotherapy groups [Kato, Y., et al 2019]. All treatments were well-tolerated and severe body weight loss was not observed.

2.2.1.4 Standard of Care

TAS-102 is a combination of trifluridine and tipiracil hydrochloride (Trifluridine/tipiracil; TAS-102; eg, LONSURF®) and will be hereafter referred to as TAS-102.

Regorafenib (BAY 73-4506; eg, STIVARGA® or REGONIX®) will be hereafter referred to as regorafenib.

Additional information on TAS-102 and regorafenib can be found in the respective prescribing information for each compound and in Section 2.2.4.

2.2.2 Preclinical and Clinical Studies

Refer to the respective IBs for preclinical and clinical study data for and lenvatinib and pembrolizumab.

This section summarizes preliminary safety and efficacy data from clinical studies of lenvatinib and/or pembrolizumab in patients with mCRC. Efficacy from these previous studies specifically in mCRC MSS is also summarized in Table 4.

2.2.2.1 Lenvatinib as Monotherapy in CRC

The LEMON (NCCH1503) clinical study, a Phase 2 study of lenvatinib in patients with mCRC refractory to standard chemotherapy including: fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab (if *RAS* WT), and TAS-102 (trifluridine/tipiracil). Prior treatment with regorafenib was not allowed. Patients received lenvatinib orally at a dose of 24 mg once daily in 28-day cycles until unacceptable toxicity or disease progression. The primary endpoint was DCR assessed by BICR. Secondary endpoints included safety, response rate, PFS, and OS. Of 30 patients enrolled, 2 patients achieved PR and 19 patients had SD, resulting in a response rate of 6.7% and DCR of 70.0% (95% CI: 50.6, 85.3%). Median PFS was 3.6 months (95% CI: 2.6, 3.7). The most common Grade ≥ 3 AEs were hypertension (53%), elevated serum AST (13%), thrombocytopenia (10%), and anorexia (7%), without unexpected safety signals [Iwasa, S., et al 2020].

2.2.2.2 Pembrolizumab as Monotherapy in mCRC that is Not MSI-H/dMMR

KEYNOTE-016 (NCT01876511) is an investigator-initiated Phase 2 Study of MK-3475 in patients with treatment-refractory advanced metastatic cancer (NCT01876511). Pembrolizumab was administered intravenously at 10 mg/kg every 14 days in patients with dMMR colorectal cancers (Cohort A), pMMR colorectal cancers (Cohort B), and dMMR cancers that were not colorectal (Cohort C). All CRC patients had received >2 prior chemotherapy regimens (median=4) except for one MSS patient who had received 1 chemotherapeutic and 1 immunotherapeutic (non-PD-1-based) regimen. The primary endpoints were immune-related ORR and 20-week immune-related PFS rate. Of the 21 patients in Cohort B, the ORR was 0% (0 of 18 patients), and the 20-week PFS rate was 11% (2 of 18 patients). The median PFS and OS, determined by Kaplan-Meier method, were 2.2 (95% CI [1.4, 2.8]) and 5.0 months (95% CI [3.0, NR]), respectively [Le, D. T., et al 2015].

2.2.2.3 Pembrolizumab Monotherapy in MSI-H/dMMR CRC

As summarized above, KEYNOTE-016 evaluated pembrolizumab monotherapy in patients with CRC who had received at least 2 prior cancer therapies. In the 40 patients with MSI-H/dMMR CRC (Cohort A), the ORR was 52% (95% CI [36, 68%]), with 5 CR. Median PFS was NR (95% CI [16.1, NR]) and median OS was NR (95% CI [NR, NR]). In patients with MSS CRC (Cohort B), no OR was observed (ORR 0%; 0/18). About 74% of patients experienced an adverse effect. Adverse events during treatment were manageable and most were low-grade. Endocrine disorders, mostly hypothyroidism, occurred in 21% of patients

and were easily managed with thyroid hormone replacement [Le, D. T., et al 2015] [Le, D. T., et al 2017].

In KEYNOTE-164, a Phase 2 open-label study (NCT02460198), 61 patients with MSI-H/dMMR mCRC, who had received at least 2 prior lines of treatment (Cohort A) were administered pembrolizumab 200 mg every 3 weeks for up to 2 years. ORR was 33% (95% CI [21%, 46%]), with 2 CR and median duration of response not reached. Median PFS was 2.3 months (95% CI [2.1, 8.1]) and median OS was 31.4 months (95% CI [21.4, NR]). In Cohort B, 63 patients had received ≥1 prior lines of therapy. ORR was 33% (95% CI [22%, 46%]), with 5 CR and median duration of response not reached. Median PFS was 4.1 months (95% CI [2.1, 18.9]) in Cohort B, and median OS was not reached (95% CI [19.2, NR]). Treatment-related Grade 3-4 AEs occurred in 10 patients (16%) in Cohort A and 8 (13%) in Cohort B, with the most common occurring in ≥ 2 patients being pancreatitis, fatigue, increased ALT, and increased lipase (2 patients each; 3%) in Cohort A [Le, D. T., et al 2019].

KEYNOTE-177 (NCT02563002) is a 2-arm, randomized, open-label, controlled Phase 3 study of pembrolizumab (monotherapy) versus standard chemotherapy in previously untreated patients who have Stage IV MSI-H or dMMR CRC. Patients were randomized in a 1:1 ratio to receive pembrolizumab (experimental arm) or the Investigator's choice of SOC chemotherapy (control arm). Pembrolizumab was superior to chemotherapy for PFS (median 16.5 vs 8.2 months; HR 0.60; 95% CI [0.45-0.80]; p=0.0002).. Grade 3-5 treatment-related AE rates were 22% versus 66% for pembrolizumab vs chemotherapy. One patient in the chemotherapy arm died due to a treatment-related AE [Andre, T., et al 2020].

Taken together, these data demonstrate a favorable safety profile of pembrolizumab in monotherapy in patients with mCRC, even in later lines of treatment.

Pembrolizumab is now approved to treat unresectable or metastatic, MSI-H/dMMR colorectal cancer in the first line of treatment in addition to later lines of treatment (refer to pembrolizumab package insert). Patients with metastatic MSI-H/dMMR CRC represent a separate subgroup of patients. Due to the efficacy benefit provided by anti-PD1 mAbs in monotherapy in this population, patients with MSI-H/dMMR mCRC will not be enrolled in LEAP-017, a Phase 3 study of pembrolizumab in combination with lenvatinib.

2.2.2.4 Lenvatinib in Combination with Pembrolizumab in CRC

LEAP-005 (E7080-G000-224) is a multicenter, open-label Phase 2 study of lenvatinib plus pembrolizumab in previously treated participants with selected solid tumors, including Cohort D CRC (not MSI-H/pMMR) who have progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Participants in LEAP-005 received pembrolizumab 200 mg Q3W and lenvatinib 20 mg QD. The primary efficacy endpoint is ORR per RECIST 1.1 by investigator assessment in the initial cohort(s), and by BICR in cohorts that expand combining initial cohort(s) and expansion cohorts(s). The key secondary endpoints are disease DCR, DOR, PFS, and OS.

As of the 10-APR-2020 data cut off, 32 patients were treated in Cohort D. Primary (ORR) and secondary efficacy outcomes (DCR and DOR) for Cohort D CRC are presented in Table 4. CCI [redacted] CCI The median follow-up for Cohort D is 6.5 months with 15 participants still on study.

All 32 patients in the CRC cohort of LEAP-005 had previously been treated for their cancer. The 21.9% ORR per BICR using RECIST 1.1 observed in the CRC cohort is numerically higher than standard therapies historically reported in this setting (~ 2%), as well as that of either lenvatinib or pembrolizumab monotherapies. Of note, the majority of these responses are ongoing as the DOR for these participants was NR (2.1+, 10.4+).

Although the safety data in this indication are limited at this time, the safety profile appears generally consistent with what has been previously observed for the combination of lenvatinib + pembrolizumab in other indications [Taylor, M. H., et al 2020] [Kawazoe, A., et al 2020] [Makker, V., et al 2020].

Recently in a Phase 1b trial a similar combination (regorafenib 80 mg plus nivolumab) showed a manageable safety profile and encouraging antitumor activity in patients with gastric and colorectal cancer. Enrolled patients received regorafenib plus nivolumab in a dose-finding part and additional patients were enrolled in a dose-expansion part. The primary end point was DLT during the first 4 weeks to estimate the RP2D. Fifty patients (25 each with gastric and colorectal cancer) were enrolled. All patients had received 2 or more previous lines of chemotherapy, including anti-angiogenetic inhibitors in 96% of patients. One patient had MSI-H/dMMR CRC, whereas the remaining patients had MSS or pMMR tumors. RP2D was determined to be 80 mg for regorafenib in combination with nivolumab. Objective tumor response was observed in 20 patients (40%), including 9 with CRC (36%). Median PFS was 7.9 months in patients CRC [Fukuoka, S., et al 2020].

In the Phase 2 REGOMUNE study of regorafenib + avelumab in mCRC that is not MSI-H/pMMR/, the combination was shown to achieve PFS and OS that compared favorably to historical data with regorafenib used as a single agent alone in a similar clinical setting [Cousin, S., et al 2020]. Median PFS was 3.6 months (95% CI, 1.8-5.4), while median OS was 10.8 months (95% CI, 5.9-NA).

Based on the promising efficacy data from LEAP-005 and the manageable safety profile observed in these patients who have limited available effective treatments and a poor survival, a Phase 3 study of lenvatinib plus pembrolizumab in comparison to SOC is warranted in patients with unresectable mCRC Stage IV, who have progressed on prior therapies.

Table 4 Summary of Efficacy Data in Studies With Monotherapy or Combination of RTKi and Anti-PD1/PD-L1 in Patients With mCRC Who Have Received and Progressed Through or Became Intolerant to Prior Treatment

	Lenvatinib LEMON Ph2	**Lenvatinib + pembrolizumab LEAP-005 Cohort D Ph2**	**Regorafenib CORRECT Ph3**	**Regorafenib + nivolumab REGONIVO Ph1b**	**Avelumab + regorafenib REGOMUNE Ph1b**
n	30	32	505	25	43
ORR[a]	6.7 (0.8-22.1)	21.9 (9.3-40.0)	1 (5/505)	33.3 (15.6-53.3)	0
DCR[a]	70 (90% CI 53.5-83.4)	46.9 (29.1-65.3)	41	80	53.5 (23/43)
PFS[b]	3.6 (2.6-3.7)	2.3 (2.0-5.2)	1.9 (IQR 1.6-3.9)	7.9 (2.9-NR)	3.6 (1.8-5.4)
OS[b]	7.4 (6.4-10.8)	7.5 (3.9-NR)	6.4 (IQR 3.6-11.8)	NR (9.8-NR)	10.8 (5.9-NR)

[a] Objective response rate (ORR) and disease control rate (DCR) in % with (95% confidence interval) unless otherwise noted.
[b] Progression free survival (PFS) and overall survival (OS) in months with (95% confidence interval) unless otherwise noted.
IQR: interquartile range; NR: not reached

2.2.3 Ongoing Clinical Studies

Refer to the respective IBs for ongoing clinical study data for lenvatinib plus pembrolizumab.

2.2.4 Information on Other Study-related Therapy

Regorafenib is a small molecule inhibitor with numerous targets, including VEGFR 1-3, PDGFRα, tyrosine receptor kinase 2, FGFRs, BRAF, KIT, and RET [Loree, J. M. 2017]. The Phase 3 CORRECT trial has established regorafenib as a SOC therapy for mCRC patients who are refractory to oxaliplatin and irinotecan-based therapy. In this study, median OS improved from 5.0 months with placebo to 6.4 months with regorafenib at a preplanned IA (HR 0.77, 95% CI 0.64–0.94, one-sided p = 0.0052) [Grothey, A., et al 2013]. The CORRECT trial results were confirmed in a broader Asian population in another Phase 3 trial, CONCUR. Regorafenib resulted in a significantly longer OS (primary endpoint) and PFS compared with placebo (HR 0.55; 95%, median 8.8 vs. 6.3 months; p = 0.00016 and HR 0.31; median 3.2 vs.1.7 months; p < 0.0001, respectively) [Li, J., et al 2015].

Regorafenib was approved in several countries for patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and, if RAS (KRAS/NRAS) wild type, with an anti-EGFR therapy.

TAS-102 is an orally administered combination of a thymidine-based nucleic acid analog, trifluridine and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. Trifluridine is the active cytotoxic component of TAS-102; its triphosphate form is incorporated into DNA, with such incorporation appearing to result in antitumor effects [Tanaka, N., et al 2014]. Tipiracil hydrochloride is a potent inhibitor of thymidine phosphorylase and, when combined with trifluridine to form TAS-102, prevents the rapid degradation of the trifluridine, resulting in the maintenance of adequate plasma levels of the active drug. The Phase 3 RECOURSE trial of TAS-102 plus best supportive care versus Placebo plus best supportive care in patients with mCRC refractory to standard chemotherapies increased OS from 5.3 months to 7.1 months compared with placebo (HR 0.68, 95% CI 0.58–0.81, p < 0.001) in treatment-refractory mCRC [Mayer, R. J., et al 2015] and was approved in several countries.

From these results, both regorafenib and TAS-102 have been recognized as standard treatments for refractory mCRC.

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 plus pembrolizumab include:

- the potential for improved OS, ORR, DOR and PFS

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

- mean decreased survival due to shorter duration of exposure to chemotherapy or VEGFR TKI
- lenvatinib and/or pembrolizumab specific side effects
- unanticipated side effects

To reduce the effects of potential side effects of the treatment combination of lenvatinib plus pembrolizumab, participants will be followed as per the SoA (Section 1.3). Detailed guidelines for dose modification and interruption are also provided in Section 6.6.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Throughout this protocol, the term RECIST 1.1 refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

In male and female participants with unresectable mCRC that is not MSI-H/dMMR who have received and progressed through or have become intolerant to prior treatment (refer to Section 5.1):

Objectives	Endpoints
Primary	
Objective: To compare lenvatinib plus pembrolizumab combination therapy to SOC with respect to OS. • Hypothesis (H1): lenvatinib plus pembrolizumab is superior to SOC with respect to OS.	OS: the time from randomization to death due to any cause.

Objectives	Endpoints
Secondary	
Objective: To compare lenvatinib plus pembrolizumab combination therapy to SOC with respect to PFS per RECIST 1.1 as assessed by BICR. • Hypothesis (H2): lenvatinib plus pembrolizumab combination therapy is superior to SOC with respect to PFS per RECIST 1.1 by BICR.	PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Objective: To compare lenvatinib plus pembrolizumab combination therapy to SOC with respect to ORR per RECIST 1.1 as assessed by BICR. • Hypothesis (H3): lenvatinib plus pembrolizumab is superior to SOC with respect to ORR per RECIST 1.1 by BICR.	Objective Response: CR or PR.
Objective: To assess the efficacy of lenvatinib plus pembrolizumab combination therapy and SOC with respect to DOR per RECIST 1.1 by BICR.	DOR, defined as the time from the first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first, in participants demonstrating CR or PR.
Objective: To evaluate the safety and tolerability of pembrolizumab plus lenvatinib versus SOC.	• AEs. • Study intervention discontinuation due to AEs.
Objective: To compare the change from baseline in global health status/QoL, physical functioning, appetite loss and bloating for the combination of pembrolizumab plus lenvatinib to SOC.	Score for the following PROs scales/items: global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).

Objectives	Endpoints
Objective: To compare the TTD in global health status/QoL, physical functioning, appetite loss and bloating for the combination of pembrolizumab plus lenvatinib to SOC.	TTD, defined as the time from baseline to the first onset of a ≥10-point deterioration from baseline in global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).
Tertiary/Exploratory	
Objective: To compare change from baseline in VAS using the EuroQoL EQ-5D-5L instrument for the combination of lenvatinib plus pembrolizumab to SOC.	Change from baseline in EQ-5D VAS.
Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab and lenvatinib.	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

4 STUDY DESIGN

4.1 Overall Design

This study is a Phase 3, randomized, controlled, 2-arm, open-label, multicenter, international, study of lenvatinib in combination with pembrolizumab versus standard chemotherapy in male and female participants with unresectable mCRC that is not MSI-H/dMMR mCRC who have received and progressed through or have become intolerant to prior treatment (refer to Section 5.1).

Participants with unresectable mCRC Stage IV as defined by AJCC eighth edition, with tumors that are not MSI-H/dMMR, with or without RAS mutations, with or without BRAF mutation, will be enrolled if they have progressed on or could not tolerate prior treatment as defined in Sections 5.1 and 5.2. No specific number of lines of prior treatment is required, providing that participants have received prior SOC treatment, as indicated per local guidelines and recommendations. The study will be stratified by presence of liver metastasis (Yes/No). The presence of liver metastasis and other sites of tumor lesions will be collected based on site radiological assessment at the screening visit. Oncologic medical history including presence of liver metastasis and prior oncologic surgeries will be collected at screening.

Approximately 434 participants will be randomized in a 1:1 ratio to receive lenvatinib in combination with pembrolizumab (Arm A) or Investigator's choice of SOC therapy (Arm B). The SOC treatment to be used in Arm B must be chosen by the Investigator between regorafenib and TAS-102 before randomization and reasons for selection of one or the other treatment will be documented. Participants will be required to have at least 1 measurable lesion per investigator assessment by RECIST 1.1 for response assessment.

In Arm A, participants will receive up to 18 administrations of pembrolizumab 400 mg Q6W (approximately 2 years). Lenvatinib treatment may continue for participants past 25 cycles until reaching a discontinuation criterion (Section 7.1).

Participants may continue treatment with lenvatinib beyond 2 years if they experience clinical benefit according to the Investigator, with Sponsor consultation and approval.

The primary endpoint for this study is OS. Secondary endpoints include safety and tolerability, PFS, ORR, DOR per RECIST 1.1 and PRO endpoints. On-study imaging assessments performed Q8W, will be calculated from the date of randomization and independent of treatment delays for both treatment arms.

For participants in the study, all disease assessments, including expedited verification of PD by BICR, will be made using RECIST 1.1. Tumor-imaging showing site-assessed PD will be submitted for verification by BICR. In Arm A, treatment beyond centrally verified PD per RECIST 1.1 may be permitted at the discretion of the investigator (if eg, no new symptoms, stable or decreasing tumor markers CEA or CA 19-9, etc.) after consultation with the Sponsor. Updated documented informed consent for continuing treatment on Arm A must be obtained prior to receiving the next study treatment. Participants in Arm B who have PD per RECIST 1.1 as verified by BICR must be discontinued from study intervention. Participants in Arm B may not crossover to Arm A intervention.

All participants will continue to be treated with study medication until PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, noncompliance with study medication or procedure requirements, administrative reasons, or a participant in Arm A has received 18 treatments (approximately 2 years).

Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE version 5.0 (Section 10.3). Each participant will be monitored for AEs for 30 days after discontinuation of study intervention, and for SAEs for 90 days after the end of study intervention or 30 days after the end of study intervention if the participant initiates new anticancer therapy, whichever is earlier.

Participants may undergo resection of the primary tumor and metastasectomy with curative intent after achieving a radiographic response to study intervention converting unresectable to resectable disease if deemed eligible per investigator's discretion in a multidisciplinary approach according to their institutional standard and following consultation with the Sponsor. Information on the resectability, site of the nodule removed and curative intent assessment during surgery will be captured on a designated CRF. In addition, participants

will be reevaluated by imaging based on RECIST 1.1 to establish a new baseline prior to potentially resuming treatment.

Following surgical resection, and at the discretion of the site Principal Investigator, participants randomized to either arm of the study may resume the same protocol-specified treatment as received preoperatively. Study treatment may resume no earlier than 6 weeks and no later than 12 weeks following surgical resection. If receiving pembrolizumab, study participants may receive up to 18 total administrations of pembrolizumab inclusive of doses administered both preoperatively and postoperatively. If receiving either regorafenib or TAS-102, postoperative study therapy may continue until radiographic disease progression has been verified by the central vendor or until intolerable adverse events preclude further administration.

Participants who discontinue study intervention for reasons other than disease progression, will have postintervention imaging follow-up for disease status Q8W (± 7 days) from date of randomization until PD (verified in an expedited manner by BICR per RECIST 1.1), start of a nonstudy anticancer therapy, consent withdrawal, becoming lost to follow-up, death, or end of the study.

All participants will be followed Q12W (± 14 days) for OS until consent withdrawal, becoming lost to follow-up, death, or end of the study.

Details regarding interim analyses are provided in Section 9.7. An eDMC will serve as the primary reviewer of the treatment-level results and will make recommendations for discontinuation or modification of the study. These recommendations will be made to an executive oversight committee of the SPONSOR. The eDMC responsibilities and review schedules will be outlined in the eDMC charter.

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

This study will be conducted in conformance with GCP.

Details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and ICF documents.

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

4.2 Scientific Rationale for Study Design

The combination of lenvatinib and pembrolizumab is being developed to treat solid tumors and hematologic malignancies.

The rationale for this randomized Phase 3 study is based on data from LEAP-005, a Phase 2 basket study where lenvatinib plus pembrolizumab was administered in single arm cohorts. Cohort D enrolled participants with mCRC who had received 2 prior lines of treatment.

The randomized, parallel design of the current study will permit to assess the safety and efficacy of the combination in comparison to SOC.

In LEAP-005 Cohort D, the combination of lenvatinib plus pembrolizumab was generally safe and well tolerated (Refer to Section 2.2.2.4). These data corroborated the acceptable safety profile of the combination reported for other indications [Taylor, M. H., et al 2020] [Kawazoe, A., et al 2020] [Makker, V., et al 2020].

Preliminary efficacy data of lenvatinib plus pembrolizumab in participants (N=32) enrolled in Cohort D of LEAP-005 showed an ORR of 21.9% (95% CI:9.3-40.0) in patients with mCRC that is not MSI-H/dMMR mCRC. The ORR is higher than that was observed with standard of care, regorafenib and TAS-102 - 1.0% and 1.6%, respectively [Grothey, A., et al 2013] [Mayer, R. J., et al 2015]. In addition, based on the mechanism of action of lenvatinib and pembrolizumab, as discussed in Section 2.2, and based on the increased ORR observed in LEAP-005, this combination appears promising in comparison to SOC in this setting.

The current study is designed as an unblinded, open-label study. Administration of placebo infusion to participants with advanced mCRC, together with additional unnecessary visits to the clinic would be an unethical burden for those participants in poor state of health. However, central review for imaging will be performed by independent radiologist(s) without knowledge of participant treatment assignment.

Participants with mCRC that is MSI-H/dMMR will not be included in this study. Local testing for MSI-H/dMMR for each participant is mandatory at Screening to confirm status.

No cross over will be allowed in the study. The primary endpoint is OS and would be confounded by participants crossing over from Arm B to Arm A.

The study will be stratified by the presence of liver metastasis (Yes/No). The effects of different prognostic factors were assessed in exploratory subgroup analysis in the RECOURSE trial [Tabernero, J., et al 2019] [Van Cutsem, E., et al 2018]. The best prognostic factor was absence of liver metastasis. Therefore, study participants will be stratified by the presence of liver metastasis (Yes/No).

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint in this trial is OS. Overall survival represents the most important and reliable endpoint to measure clinical efficacy in a population of patients with unresectable mCRC who have received and progressed on or after or became intolerant to fluoropyrimidine, irinotecan, oxaliplatin and other SOC treatment (refer to Sections 5.1 and 5.2).

Standard of care in later lines of treatment, such as regorafenib and TAS-102, are associated with median OS of only 6.4 and 7.1 months in these patients, respectively [Grothey, A., et al 2013] [Mayer, R. J., et al 2015].

The sample size is estimated based on the primary endpoint of OS, and the required target number of events to detect the superiority of lenvatinib plus pembrolizumab treatment versus standard of care in the comparison of OS.

The secondary efficacy endpoints will include PFS, ORR and DOR per RECIST 1.1 as assessed by BICR and PROs as assessed by the EORTC QLQ-C30 and EORTC QLQ-CR29, which are standard questionnaires utilized in this population of patients with mCRC. These endpoints are commonly accepted endpoints by both regulatory authorities and the oncology community. Objective response rate was not chosen as the primary endpoint, as OS represents a more complete assessment of the clinical benefit experienced by these patients. Overall survival has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

The use of BICR and RECIST 1.1, to assess PFS, ORR and DOR is considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by BICR to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on BICR, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression as determined by BICR will be communicated to the site and Sponsor.

Exploratory endpoints will include additional PRO measures as assessed by the EQ-5D-5L questionnaire.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.4 for additional detail.

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version [5.0].

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. As part of the analyses for this study, health-related quality of life (HRQoL) and disease-related symptoms will be investigated among all participants via the following assessment tools: EORTC QLQ-C30 and the EuroQol EQ-5D-5L questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. PRO instruments will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 and EQ-5D-5L. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30 and EORTC QLQ-CR29

The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing HRQoL in oncology studies [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [Aaronson, N. K., et al 1993]. For the global health status or QoL and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. Time to true deterioration, mean change from baseline in global health status or QoL, physical functioning and appetite loss scale of the EORTC QLQ-C30, will be evaluated as secondary objectives.

The EORTC QLQ-CR29, a supplemental colorectal cancer-specific module, comprises multi-item and single-item measures of colorectal cancer-associated symptoms and impact. It includes 4 scales assessing urinary frequency, fecal seepage, stool consistency, and body image, and single items assessing other common problems following CRC therapy. Specific questions are also to be answered if participants have / do not have a stoma bag to assess any impact on HRQoL or symptoms. Time to deterioration and mean change from baseline in bloating scale of the EORTC QLQ-C29, will be evaluated as secondary objectives.

4.2.1.3.2 EuroQoL EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension

is rated on a 5 point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates their general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

The EQ5D-5L will always be completed by participants first before completing the EORTC QLQ-C30 and EORTC QLQ-CR29. All questionnaires are to be completed at various time points as specified in the SoA in Section 1.3.

4.2.1.4 Pharmacokinetic Endpoints

To reduce the burden to the participants, there will be no pharmacokinetic or ADA studies performed in this study, as the PK profile for the combination of pembrolizumab and lenvatinib and the ADA to pembrolizumab have been previously characterized. Please see the respective IBs for more details.

4.2.1.5 Pharmacodynamic Endpoints

There will be no pharmacodynamic studies performed in this study.

4.2.1.6 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. CCI

CCI

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. CCI

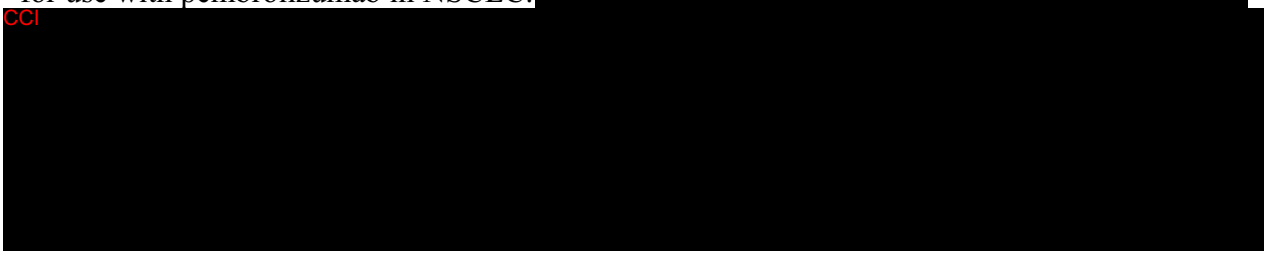
CCI

CCI

Proteomics and IHC using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. CCI

CCI



Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's

reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

4.2.2 Rationale for the Use of Comparator

Regorafenib and TAS-102 are considered SOC globally for patients with mCRC whose disease is refractory to fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, as recommended by formal guidelines [Chiorean, E. G., et al 2020] [Hashiguchi, Y., et al 2020] [Van Cutsem, E., et al 2014] [National Comprehensive Cancer Network 2020] [Sepulveda, A. R., et al 2017]. Therefore, study treatment in the comparator arm (Arm B) in this study will be physician's choice of regorafenib or TAS-102.

4.3 Justification for Dose

4.3.1 Lenvatinib

The dosing regimen of lenvatinib was selected based on the results of the Phase 1b portion of Phase 1b/2 Study 111/KEYNOTE-146, the primary endpoint of which was to determine the MTD and RP2D for lenvatinib in combination with pembrolizumab 200 mg Q3W. Thirteen participants (lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W: n=3; lenvatinib 20 mg/day + pembrolizumab 200 mg: n=10) were enrolled in the Phase 1b portion of the study. Eight of the participants had RCC, 2 had NSCLC, 2 had endometrial carcinoma, and 1 had melanoma. There were 2 DLTs at the dose of lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W (1 participant had Grade 3 arthralgia, and another had Grade 3 fatigue); hence, this was defined as the toxic dose. No DLTs were reported in the next 10 participants (expansion part), all of whom received the lenvatinib 20 mg/day + pembrolizumab 200 mg Q3W dose.

Based on review of all of the clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib daily in combination with a fixed dose of 200 mg pembrolizumab given Q3W. CCI

CCI

In mCRC, the safety data of lenvatinib in combination with pembrolizumab in this indication are limited. Based on IA1 in LEAP-005 Cohort D, the safety profile appears generally consistent with what has been previously observed for the combination of pembrolizumab + lenvatinib in other indications (Section 2.2.2.4). Based on the promising efficacy data and the manageable safety profile observed in this patient population with limited available effective treatments and a poor survival, the starting dose of lenvatinib at 20mg QD is justified.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 400 mg Q6W.

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

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 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on Modeling & Simulation 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.
- Trough concentrations (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.
- Peak concentrations (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.
- E-R 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.

4.3.3 Maximum Dose/Exposure for This Study

4.3.3.1 Arm A

The maximum dose/exposure of lenvatinib allowed in this study is 20 mg QD. The maximum dose/exposure of pembrolizumab allowed in this study is 400 mg Q6W up to 18 administrations. Participants may continue treatment with lenvatinib if they experience clinical benefit according to the Investigator with Sponsor consultation until disease progression or unacceptable toxicity.

4.3.3.2 Arm B

Doses for regorafenib or TAS-102 used in this study are defined based on prescribing information and local guidelines (Refer to Section 6.1 and Table 6). Please refer to package inserts and local guidelines for maximum used dose, overdosage and corresponding guidelines for regorafenib and TAS-102.

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 (ie, the participant is unable to be contacted by the investigator).

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

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory 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 EAA is defined as First Site Ready (FSR) in any Member State.

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.

Early trial termination criteria:

- The clinical trial may be stopped for a safety reason at the recommendation of the eDMC.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has histologically or cytologically confirmed diagnosis of unresectable and metastatic colorectal adenocarcinoma (Stage IV A, B and C as defined by AJCC 8th edition).

   Note: Tumor must be determined to be NOT MSI-H/dMMR by local testing.

2. Has been previously treated for their disease and has shown disease progression as defined by RECIST 1.1 on or after, or could not tolerate standard treatment, which must

include ALL of the following agents if approved and locally available in the country where the participant is randomized:

Note: Adjuvant chemotherapy counts as prior systemic therapy if there is documented disease progression within 6 months of chemotherapy completion.

Note: A participant who has withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study. If a participant is determined to be intolerant to a prior line of therapy, the participant must have had a minimum of 2 cycles of that therapy.

a. Fluoropyrimidine, irinotecan and oxaliplatin.

   Note: Capecitabine is acceptable as equivalent to fluoropyrimidine in prior therapy (XELOX/CAPOX and XELIRI are considered equivalent to FOLFOX and FOLFIRI, respectively).

   Note: Participants who have previously received fluoropyrimidine, oxaliplatin, and irinotecan as part of the same and only chemotherapy regimen, e.g., FOLFOXIRI or FOLFIRINOX, may participate the study.

b. With or without an anti-VEGF monoclonal antibody (bevacizumab)

c. With anti-EGFR mAbs (cetuximab or panitumumab) for RAS (KRAS/NRAS) WT participants.

   Note: RAS (KRAS/NRAS) WT participants with right or left CRC lesions who may have not been treated based on local guidelines with anti-EGFR mAbs are eligible.

   Note: For participants with ctDNA RAS mutant, but RAS mutation negative in tissue, enrollment into the study before anti-EGFR mAbs administration is allowed.

d. BRAF inhibitor (in combination with cetuximab +/- binimetinib) for BRAF V600E mutated mCRC.

3. Has measurable disease per RECIST 1.1 assessed by the investigator.

   Note: Participants with brain metastases are not eligible to be enrolled.

4. Has provided to a designated central laboratory an archival tumor tissue sample or newly obtained core, incisional or excisional biopsy of a tumor lesion which has not been previously irradiated. Formalin-fixed, paraffin embedded tissue blocks are preferable to slides. Newly obtained biopsies are preferable to archived tissue. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

5. Has an ECOG performance status of 0 to 1 within 3 days prior to randomization.

6. Has a life expectancy of at least 3 months, based on the investigator assessment.

7. Has the ability to swallow capsules or ingest a suspension orally or by a feeding tube.

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

9. Has adequate organ function as defined in the following Table 5. Specimens must be collected within 3 days prior to the start of study intervention.

Table 5 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Albumin	≥3 g/dL[3]
Coagulation	
INR or PT aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); ANC=Absolute neutrophil count; aPTT=Activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; INR= International normalized ratio; PT= prothrombin time; ULN=upper limit of normal.

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

[2] Creatinine clearance (CrCl) should be calculated per institutional standard.

[3] Albumin infusion will not be allowed for 14 days before enrollment into the study

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

Demographics

10. Is male or female ≥18 years of age at the time of providing documented informed consent.

Male Participants

11. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of regorafenib or TAS-102 and at least 7 days after the last dose of lenvatinib:

    - Refrain from donating sperm

      PLUS either:

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

      OR

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

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

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

      - The male contraception period should continue for at least 7 days after discontinuation of lenvatinib. Please note that 7 days after lenvatinib is stopped, if the participant is on pembrolizumab only, no male contraception measures are needed.

    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.

Refer to Appendix 7 for country-specific requirements.

Female Participants

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

    - Is not a WOCBP

      OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 30 days after the last dose of lenvatinib, 120 days after the last dose of pembrolizumab (whichever is last), and 180 days after the last dose of regorafenib or TAS-102 and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

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

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

    - Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5 and Appendix 5.

    - Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.

    - 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 interventions is more stringent than the requirements above, the local label requirements are to be followed.

Refer to Appendix 7 for country-specific requirements.

Informed Consent

13. The participant (or legally acceptable representative if applicable) provides documented informed consent/assent for the study.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has a tumor that is MSI-H/dMMR per local testing.

2. Has presence of gastrointestinal condition, eg, malabsorption, that might affect the absorption of study drug.

3. Has present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment. The participant can receive diuretic drugs as needed per the treating physician, outside of the above-mentioned conditions.

4. Has radiographic evidence of encasement or invasion of a major blood vessel invasion, or of intratumoral cavitation. In the chest, major blood vessels include the main pulmonary artery, the left and right pulmonary arteries, the 4 major pulmonary veins, the superior or inferior vena cava, and the aorta,

   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 following lenvatinib therapy.

5. Has clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

6. 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: Participants with cardiac failure NYHA Class II, III and IV are not allowed to be assigned to the regorafenib in Arm B.

   Note: Medically controlled arrhythmia would be permitted.

7. Has a history of arterial thromboembolism within 12 months of start of study drug.

8. Has urine protein ≥1 g/24h.

   Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria.

9. Has prolongation of QTcF interval to >480 ms.

10. Has LVEF below the institutional (or local laboratory) normal range as determined by MUGA or ECHO.

11. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Exceptions include early-stage cancers (carcinoma in situ or stage 1, non-ulcerated primary melanoma <1 mm in depth with no nodal involvement) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or in situ breast cancer that has undergone potentially curative therapy.

12. Has serious nonhealing wound, ulcer or bone fracture.

13. Has had major surgery within 3 weeks prior to first dose of study interventions.

    Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention. Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

14. Has received biologic response modifiers (eg, granulocyte colony-stimulating factor) within 4 weeks before study entry. Chronic erythropoietin therapy is permitted provided that no dose adjustments were made within 2 months before first dose of study treatment.

15. Has preexisting ≥Grade 3 gastrointestinal or nongastrointestinal fistula.

Prior/Concomitant Therapy

16. Has received prior treatment with a combination of an anti-PD-1, anti-PD-L1, or anti PD-L2 agent with anti-VEGF mAbs or VEGFR inhibitors.

    Note: Participants who have received an anti-PD-1, anti-PD-L1, or anti PD-L2 agent in combination with an anti-CTLA-4 agent as a prior line of treatment, are eligible.

    Note: Participants who have received an anti-PD-1, anti-PD-L1, or anti PD-L2 agent in combination with anti-VEGF mAbs or VEGFR inhibitors in combination with chemotherapy are not eligible.

17. Has previously received regorafenib or TAS-102.

18. Has received prior systemic anti-cancer therapy including investigational agents within 28 days prior to randomization.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

19. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

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

    Refer to Section 6.5.1 for information on COVID-19 vaccines.

21. Has known intolerance to lenvatinib, regorafenib or TAS-102 and/or any of their excipients.

    Note: Participants receiving inhibitors or inducers of CYP3A and BCRP substrates should not receive regorafenib in Arm B.

Prior/Concurrent Clinical Study Experience

22. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 28 days 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 28 days after the last dose of the previous investigational agent.

Diagnostic Assessments

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

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

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

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

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

28. Has an active infection requiring systemic therapy.

29. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.

30. 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.

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

31. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

Other Exclusions

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

Participants randomized to regorafenib should avoid food containing strong CYP3A4 inducers, strong CYP3A4 inhibitors as per local guidelines and regulations.

5.3.2 Contraception

Study interventions in Arm A and Arm B may have adverse effects on a fetus *in utero*. Refer to Appendix 5 for approved methods of contraception.

5.3.3 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.4 Activity Restrictions

No restrictions are required.

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

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 (lenvatinib and/or pembrolizumab and/or regorafenib and/or TAS-102) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 6.

Table 6 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm A	Experimental	Lenvatinib	Drug	Capsule	10 mg 4 mg	20 mg	Oral	QD	Test Product	IMP	Centrally by Sponsor
Arm A	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	400 mg	IV Infusion	Q6W	Test Product	IMP	Centrally by Sponsor
Arm B	Active Comparator	Regorafenib	Drug	Tablet	40 mg/tablet	160 mg	Oral	Q4W (QD Days 1-21, no dose Days 22-28)	Comparator	IMP	Centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Arm B	Active Comparator	TAS-102	Drug	Tablet	15 mg trifluridine/ 6.14 mg tipiracil 20 mg trifluridine/ 8.19 mg tipiracil	35 mg/m^2	Oral	Q4W (BID Days 1-5 and Days 8-12, no dose Days 6-7, or Days 13-28)	Comparator	IMP	Centrally by the Sponsor or locally by the trial site, subsidiary, or designee

Abbreviations: AxMP = auxiliary medicinal product; BID=twice daily; IMP= investigational medicinal product; IV= intravenous; mg=milligram mL=milliliter; NIMP= non investigational medicinal product; Q4W= every 4 weeks; Q6W= every 6 weeks; QD=daily

The classification of Investigational Medicinal Product (IMP), Auxiliary Medicinal Product (AxMP) and Non-Investigational Medicinal Product (NIMP) 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 or NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 6 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

6.2.1.1 Lenvatinib

Lenvatinib is a capsule for oral administration and does not require preparation. Details on administration of lenvatinib 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.

If a dose of lenvatinib is missed and cannot be taken within 12 hours from the scheduled administration, the participant should skip this dose and take the next dose at the scheduled time the next day. See Pharmacy Manual for additional information.

6.2.1.2 Pembrolizumab

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

6.2.1.3 Regorafenib

Regorafenib will be prepared and administered as per the approved product label and should follow local therapeutic guidelines. According to local/institutional guidelines, regorafenib may be administered as follows in Cycle 1: 80 mg regorafenib QD on Cycle 1 Days 1 to 7, then 120 mg QD on Days 8 to 14, followed by 160 mg QD on Days 15 to 21, and 160 mg QD on subsequent cycles (Days 1 to 21) [Bekaii-Saab, T. S., et al 2018].

Participants are advised to swallow the regorafenib tablet whole with water at the same time each day following a low-fat meal. Refer to local guidelines and regulations for more details.

Any missed dose or regorafenib should be taken on the same day, as soon as the participant remembers, although 2 doses should not be taken on the same day to make up for a dose missed on the previous day. Refer to local guidelines and regulations for more details.

6.2.1.4 TAS-102

TAS-102 will be prepared and administered as per the approved product label and should follow local therapeutic guidelines. The BSA in m^2 should be calculated per local guidance. The dose of TAS-102 should be recalculated for fluctuation of body weight ≥10% at the beginning of a cycle only. For weight fluctuation <10%, recalculation may be done at the discretion of the investigator. When recalculating, BSA in m^2 should be calculated per local guidance.

Participants in Arm B should be advised to take TAS-102 with food. Participants or anyone else who handles their medication should be advised to wear gloves as per local guidelines and regulations.

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

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 study intervention (Arm A) or physician's choice of SOC (Arm B).

The SOC treatment to be used must be chosen by the Investigator between regorafenib and TAS-102 before randomization and reasons for selection of one or the other treatment will be documented.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factor, as described in Section 4.2:

- Presence of liver metastasis (Yes/No)

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, Investigator and participant will know the treatment administered.

Imaging data will be centrally reviewed by independent radiologist(s) without knowledge of participant treatment assignment.

6.4 Study Intervention Compliance

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

Lenvatinib, regorafenib, and TAS-102 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.

Interruptions from the protocol specified intervention plan for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc, during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of lenvatinib capsules or regorafenib tablets or TAS-102 tablets dispensed to and taken by each participant must be maintained and reconciled with study

intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.4.1 Arm A

Lenvatinib: On the day of a clinic visit lenvatinib will be taken at the clinic after laboratory assessment. On the day of pembrolizumab administration, lenvatinib will be taken in the clinic, 0 to 4 hours after pembrolizumab infusion (Refer to Section 1.3). For all other days lenvatinib will be taken at home.

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

Refer to Section 6.6.1 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruption of pembrolizumab.

6.4.2 Arm B

For Arm B, the first dose of Cycle 1 SOC (regorafenib or TAS-102) must be given to the participant at the site and will be witnessed by the investigator and/or study staff, and/or qualified designee per institutional guidelines and procedures. For medication taken at home, the site will validate compliance with study medication at each site visit according to their standard operating procedure.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator is to discuss prohibited medication/vaccination 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.

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.

All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

6.5.1 Prohibited Concomitant Medication(s)

6.5.1.1 Arm A Prohibited Concomitant Medication(s)

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

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

  Note: Radiation for pain or palliation treatment may be acceptable (in case of target lesion, please refer to the imaging manual and charter to the iCRO)

- Live or live-attenuated vaccines within 30 days before 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, replication-incompetent 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 of an AE that is suspected to have an immunologic etiology.

  - As needed for the prevention of emesis.

  - Premedication for IV contrast allergies.

  - Short-term oral or IV use in doses >10 mg/day prednisone equivalent to treat asthma or COPD exacerbations.

  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent.

- In addition, the following glucocorticoid use is allowed:
  - For topical use or ocular use.
  - Intraarticular joint use.
  - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

6.5.1.2 Arm B Prohibited Concomitant Medication(s)

Restriction on the use of concomitant drug during administration of regorafenib or TAS-102 should follow the local guidelines and regulations (see the respective regorafenib or TAS-102 package inserts for more information).

6.5.2 Drug Interactions

6.5.2.1 Arm A Drug Interactions

There are no DDI-related concomitant medication prohibitions or restrictions. Lenvatinib is not expected to clinically meaningfully alter exposure to CYP3A4/P-gp substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and P-gp substrate). Clinical studies also showed that coadministration of lenvatinib with either inducers or inhibitors of CYP3A4/P-gp are not of clinical concern.

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

Use medicinal products with known potential to prolong the QT/QTc interval with caution when coadministered with lenvatinib.

6.5.2.2 Arm B Drug Interactions

During administration of regorafenib, avoid concomitant use of strong CYP3A4 inducers, strong CYP3A4 inhibitors, and BCRP substrate as recommended by local guidelines and regulations (see regorafenib package insert). Monitor participants closely for signs and symptoms of exposure-related toxicity when concomitant use with these compounds.

Local guidelines for TAS-102 should be followed, as well as information contained in the TAS-102 package insert.

6.5.3 Rescue Medications and Supportive Care

The investigator should follow institution guidelines for use of supportive care in participants treated with standard of care. For participants in Arm A receiving lenvatinib plus pembrolizumab, suggested supportive care measures for the management of AEs with

potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6, Table 7. 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 lenvatinib or pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 7 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

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

Participants in Arm B should receive appropriate supportive care measures as deemed necessary by the treating investigator. The investigator should follow institution guidelines for use of supportive care in participants treated with regorafenib or TAS-102.

6.6 Dose Modification (Escalation/Titration/Other)

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

Participants in Arm A who interrupt or discontinue one drug in the lenvatinib-pembrolizumab combination due to toxicity can continue with the other drug in the combination until criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression).

Refer to Section 6.6.3 for dose modification guidance for overlapping toxicity for the pembrolizumab plus lenvatinib combination.

For participants in Arm B, refer to the labeling or local guidelines for dose modification for regorafenib or TAS-102.

6.6.1 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 7.

Table 7 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	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
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).

6.6.1.1 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 8.

Table 8 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 Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 6 weeks of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.2 Dose Modification and Toxicity Management Related to Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 9. An interruption of lenvatinib for more than 28 days regardless of etiology will require Sponsor approval before treatment can be resumed.

Asymptomatic laboratory abnormalities, including Grade ≥3 abnormalities (eg, elevations of amylase and lipase) that are not considered clinically relevant by the investigator should be managed per institutional guidelines; continuation of treatment should be discussed with the Sponsor.

The starting dose of lenvatinib is 20 mg/day. Dose reductions of lenvatinib occur in succession based on the previous dose level 14, 10, 8 mg/day. Any dose reduction below 8 mg/day must be discussed with the Sponsor. Once the lenvatinib dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Refer to the subsections below for management of hypertension (Section 6.6.2.1), proteinuria (Section 6.6.2.2), diarrhea (Section 6.6.2.3), hepatotoxicity (Section 6.6.2.4), thromboembolic events (Section 6.6.2.5), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 6.6.2.6), hypocalcemia (Section 6.6.2.7), hemorrhage (Section 6.6.2.8), gastrointestinal perforation or fistula formation (Section 6.6.2.9), QT prolongation (Section 6.6.2.10) and osteonecrosis of the jaw (Section 6.6.2.11) as appropriate, before consulting the dose modification Table 9. For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.3.

Table 9 Dose Modification Guidelines for Lenvatinib-Related Adverse Events

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e, f]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction) /
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction) /
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction) /
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[g]: Discontinue Study Treatment		

Abbreviations: AE = adverse event; BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events.

Note: For grading see CTCAE version 5.0. Collect all AE grades (i.e., decreasing and increasing CTCAE grade).

a. An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.

b. Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhoea prior to any lenvatinib interruption or dose reduction.

c. Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.

d. Obese participants (BMI ≥30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they have a minimum BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.

e. For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.

f. For Grade 3 thromboembolic event, permanently discontinue lenvatinib/matching placebo. See Section 6.6.1.5.

g. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

6.6.2.1 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).

If the participant's first BP measurement of the current assessment is elevated (i.e., 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 (i.e., 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 (eg, BP ≥160/100 mm Hg) with significant risk factors for severe complications, 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 the Day 15 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:

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 drug

6.6.2.2 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 or urinalysis per the SoA (Section 1.3.1). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipsticks 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 (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).

3. A 24-hour urine collection (initiated as soon as possible and at least within 72 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 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 9.

Monitoring

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.

- 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

6.6.2.3 Management of Diarrhea

An anti-diarrheal agent should be recommended to the participant at the start of study treatment, and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal 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 9 should be followed.

6.6.2.4 Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the SoA (Section 1.3.1) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 9. should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v5) occurs, lenvatinib must be discontinued.

6.6.2.5 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, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case 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 9 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 reaction, 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 study treatment discontinuation.

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

Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome 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. Magnetic resonance imaging 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 9 should be followed.

6.6.2.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3.1). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

$$\text{Corrected calcium} = ([4 - \text{serum albumin in g/dL}] \times 0.8 + \text{serum calcium})$$

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.

6.6.2.8 Management of Hemorrhage

Instructions in Table 9 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.

6.6.2.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or Grade 4 fistula.

6.6.2.10 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.

6.6.2.11 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 6.6.4).

6.6.3 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and lenvatinib, 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 immune-related AEs are risks for pembrolizumab treatment.

However, certain AEs, such as 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

   Since lenvatinib is 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 (i.e., interruption of treatment) based on the following 2 scenarios:

   - If an AE is identified during a treatment cycle (i.e., 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 (i.e., 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, TIDM) and other supportive care should be taken promptly.

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

   - ALT or AST >5 X ULN for more than 2 weeks.
     Pembrolizumab will have already been permanently discontinued per Table 7, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
   - ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5).
     Although Table 7 advises pembrolizumab to be withheld (interrupted), 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 Other Allowed Dose Interruptions

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.

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. However, pembrolizumab is to be started within 42 days of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. In case of surgery (including surgery for curative intent), pembrolizumab must resume at least 6 weeks and no more than 12 weeks post-surgery, if clinically appropriate. Participants may receive up to 18 total administrations of pembrolizumab inclusive of both preoperative and postoperative periods. The reason for pembrolizumab interruption is to be documented in the participant's study record.

For regorafenib or TAS-102, instructions for stop time and restart time for dose interruptions should follow the regulation and local guidelines. In case of surgery (including surgery for curative intent), regorafenib or TAS-102 must resume at least 6 weeks and no more than 12 weeks post-surgery, if clinically appropriate.

6.7 Intervention After the End of the Study

There is no study-specified intervention following 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 regimen will still continue to be monitored in this study and participate in the study visits and procedures 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.

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.
- After prolonged study intervention interruption that prohibits restarting study intervention as agreed upon with the Sponsor.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1.4 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Initiation of a new anticancer treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

Participants must discontinue study therapy if any of the following occur:

ALT or AST elevation meeting the following criteria:

- ALT or AST >5 × ULN for more than 2 weeks
  Note: In Arm A, pembrolizumab will have already been permanently discontinued per Table 7, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

- ALT or AST >3 × ULN and (TBL >2X ULN or INR > 1.5)
  Note: In Arm A, although Table 7 advises pembrolizumab to be withheld (interrupted), 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.

Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Sec. 6.6. require sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.

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 or 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 utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will be provided 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. 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 trial protocol number, trial protocol title, dated signature, and agreement of the participant (or his/her 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 his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's 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.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria in Section 5.1 and Section 5.2 will be reviewed by the investigator, who is a qualified physician, to ensure that the participant is eligible for the study.

8.1.3 MSI-H/dMMR Local Testing and Biopsy Sample

Results from local testing for MSI-H/dMMR status (eg, per IHC and/or PCR) are mandatory at entry (see Section 5.1) and will be collected in the corresponding CRFs. Participants whose tumors are MSI-H/dMMR are not eligible for the study.

Additionally, an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion is required for entry in the study (see Section 5.1) and will be shipped to a designated central laboratory (see Laboratory Manual).

8.1.4 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 allocation, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.5 Medical History

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

If a medical condition is diagnosed at the time of Screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in).

8.1.6 Oncologic Disease Medical History

The investigator or qualified designee will obtain specific medical history 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, where applicable. History of Lynch syndrome needs to be described if known.

8.1.7 Prior and Concomitant Medications Review

8.1.7.1 Prior Medications

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

8.1.7.2 Concomitant Medications

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

8.1.7.3 Prior Oncologic Treatment

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

8.1.8 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.8.1 Treatment Eligibility Assessment Form

A TEA form is included in this study to document the investigator assessment of participant suitability for potential treatment in Arm B with regorafenib or TAS-102 and the rationale.

The investigator must complete this form and provide rationale to document the choice of regorafenib or TAS-102 prior to randomization.

8.1.9 Assignment of Treatment/Randomization Number

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

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

8.1.10 Study Intervention Administration

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

It is strongly preferred that participants receive first dose of study intervention on day of randomization.

The first dose of Cycle 1 of oral study drug (lenvatinib or regorafenib or TAS-102) must be taken by the participant while at the site.

Refer to the Pharmacy Manual for lenvatinib and pembrolizumab administration for Arm A.

Refer to the regorafenib or TAS-102 product label, respectively, for guidance on administration procedures for regorafenib or TAS-102, for Arm B.

Study intervention should begin within 3 days of randomization.

8.1.10.1 Timing of Dose Administration

Study treatment in both arms will follow a 28-day cycle and will begin after all procedures/assessments have been completed as detailed in the SoA (Section 1.3). Study treatments may be administered up to 3 days after Cycle 1 Day 1 and up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

All study treatments may be administered on an outpatient basis.

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, achievement of a CR, or administrative reasons requiring cessation of treatment.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (eg, 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. Discuss with the Sponsor if participants cannot restart study medication within 12 weeks for pembrolizumab, 4 weeks for Lenvatinib and 3 weeks for Arm B treatment. The reason for interruption should be documented in the participant's study record.

Study treatment should be discontinued in Arm A if the participant interrupts study intervention administration for more than 12 weeks of pembrolizumab AND 4 weeks of lenvatinib, except if agreed to by the Sponsor. In Arm B, study treatment interruptions and/or treatment discontinuation will be followed per local guidelines and label, if beyond 3 weeks contact Sponsor.

The dose and schedule modifications of study interventions are provided in Section 6.6 – Dose Modification.

8.1.10.1.1 Arm A

8.1.10.1.1.1 Lenvatinib Administration

Lenvatinib is provided as 4 mg or 10 mg capsules. Lenvatinib 20 mg once daily will be taken orally with water (with or without food) at approximately the same time each day in each 28-day cycle. However, on day of pembrolizumab administration (approximately every 6 weeks) lenvatinib will be administered 0 to 4 hours after completion of pembrolizumab administration at the clinic.

If a lenvatinib dose is missed and cannot be taken within 12 hours of planned administration, that dose should be skipped and the next dose should be taken at the usual time of administration

Details on preparation and administration of lenvatinib are provided in the Pharmacy Manual.

8.1.10.1.1.2 Pembrolizumab Administration

Pembrolizumab will be administered as a 30-minute IV infusion Q6W according to SoA (Section 1.3). 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 30 minutes: -5 min/+10 min).

After Cycle 1 Day 1, pembrolizumab may be administered up to 3 days before or after the scheduled treatment day of each subsequent cycle due to administrative reasons.

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

8.1.10.1.2 Arm B

8.1.10.1.2.1 Regorafenib Administration

Participants are to take regorafenib at the same time each day on Days 1 to 21 of each cycle. Participants are to swallow the tablets whole with water after a meal. Participants are not to take 2 doses of regorafenib on the same day to make up for a missed dose from the previous day. Participants are not to take any doses of regorafenib on Days 22 to 28 of each cycle. Refer to the regorafenib package insert for current prescription information.

8.1.10.1.2.2 TAS-102 Administration

Participants are to take TAS-102 twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. Participants are to swallow the tablets whole with water after a meal. Participants are not to take 2 doses of TAS-102 at once to make up for a missed dose. Participants are not to take any doses of TAS-102 on Days 6 and 7 and 13 to 28 of each cycle. Refer to the TAS-102 package insert for current prescription information. For

calculation of TAS-102 dosing based on weight/BSA, refer to the website PPD

8.1.10.2 Compliance

8.1.10.2.1 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 capsules.

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.

8.1.10.2.2 Pembrolizumab

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

8.1.10.2.3 Regorafenib

During onsite visits, regorafenib will be administered by the investigator and/or study staff according to the specifications within the product label and local guidelines. 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, regorafenib will be taken at home. When a participant attends a study visit, he or she will bring any unused tablets as per protocol.

Regorafenib 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.

8.1.10.2.4 TAS-102

During onsite visits, TAS-102 will be administered by the investigator and/or study staff according to the specifications within the product label and local guidelines. 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, TAS-102 will be taken at home. When a participant attends a study visit, he or she will bring any unused tablets as per protocol.

TAS-102 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.

8.1.11 Discontinuation and Withdrawal

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

8.1.12 Participant Blinding/Unblinding

This is not applicable as this is an open-label study.

8.1.13 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.

8.1.14 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required and is to be:

- A newly obtained core, incisional or excisional biopsy of a tumor lesion, which was not previously irradiated

  Or

- An archival tumor tissue sample if a new biopsy is unavailable

If obtained at Screening, the procedure should be performed before screening /baseline scans are performed.

Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx diagnostic kit except it is labeled IUO. The PD-L1 IHC 22C3 pharmDx assay kit is currently approved to assess PD-L1 status.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or enters the survival follow-up. The process for scan collection and transmission to the iCRO can be found in the SIM. CT scans are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same type of scan 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 response assessment. Note: for the purposes of assessing tumor scans, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Participant eligibility will be determined using investigator assessment based on RECIST 1.1. All scheduled scans for each participant from the sites will be submitted to the iCRO. In addition, unscheduled scans to determine disease progression, and scans obtained for other reasons, but captures radiologic progression based on investigator assessment, are to be submitted to the iCRO.

If brain scans are performed, magnetic resonance scans are preferred; however, CT scans are acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans done to support a positive or negative bone scan, such as plain X-rays acquired for correlation, should also be submitted to the iCRO.

Other imaging modalities that may be collected, submitted to the iCRO, and included in the response assessment include chest x-rays, etc. Other types of scans (eg, ultrasound) should not be submitted to the iCRO and will not be included in response assessment.

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 scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site 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.

If brain scans are required to document the stability of existing metastases, the brain scan MRI should be acquired during screening. The specific methods permitted for this study are described in the SIM.

Bone scans are required at screening for participants with a history of bone metastases and/or for those participants with indicative clinical signs/symptoms such as bone pain or elevated alkaline phosphatase levels.

Bone scan refers to imaging methods used to assess bone metastasis. The specific methods permitted for this study are described in the SIM.

Tumor scans performed as part of routine clinical management are acceptable for screening if they are of acceptable diagnostic quality and performed within 28 days prior to randomization.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 8 weeks (56 days ±7 days) from the date of randomization. Subsequent tumor scans should be performed every 8 weeks (56 days ±7 days) or more frequently if clinically indicated. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Scans should continue 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, whichever occurs first. All supplemental scans must be submitted 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 time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

For participants who have surgery with curative intent during the study, scans must be performed at a minimum of no less than 4 weeks after surgery and no more than 8 weeks prior to the next treatment cycle. The last set of scans prior to restart of treatment will be used to establish a new baseline of tumor burden. Subsequent scans will be compared to this new baseline and the visit responses will be limited to PD, non-PD, or NE (not evaluable);

these new postoperative images will be assessed every 8 weeks (56 days ± 7 days) for 12 months and every 12 weeks (84 days ± 7 days) thereafter.

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

Treatment beyond centrally verified PD per RECIST 1.1 may be permitted in Arm A at the discretion of the investigator after consultation with the Sponsor and receiving documented informed consent. Participants who continue treatment beyond centrally verified PD must continue tumor assessments as described in the SoA (Section 1.3). Investigator assessments are to be documents on the eCRF, but scans are not to be submitted to the iCRO. Further progression and discontinuation of study intervention are to be determined by the investigator.

When the investigator identifies radiographic progression per RECIST 1.1, the iCRO will perform expedited verification of radiologic disease progression and communicate the results to the study site and Sponsor via email. In clinically stable participants, scans should continue until disease progression has been verified by BICR (if initial site-assessed disease progression was not verified by BICR, each subsequent scan must be submitted to iCRO with verification of disease progression request until disease progression has been verified by BICR). Once disease progression is verified centrally, subsequent scans (if acquired) should not be submitted to the iCRO.

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

If participants discontinue study intervention, tumor scans should be performed at the time of 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.

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

8.2.1.4 RECIST 1.1 Assessment of Disease

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

Upon investigator-assessed disease progression, the indicative scan(s) are to be submitted immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

CCI

[redacted]

CCI

8.2.2 Patient-reported Outcomes

The EuroQoL EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-CR29 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EuroQoL EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-CR29. The questionnaires should be administered prior to dosing at Day 1 and Day 15 of C1 through C3 and then Day 1 of C4 through C12 and then Day 1 of every other cycle thereafter (ie, C14, C16, etc. up to C26) up to 2 years until end of treatment or treatment discontinuation, whichever occurs first, and at the 30-day posttreatment safety follow-up visit.

It is best practice and strongly recommended that ePROs are administered to randomized participants prior to drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

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

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

8.3.1.2 Directed Physical Examination

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

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

8.3.2 Vital Signs

- Vital signs will be measured in a semisupine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.
- Blood pressure and pulse measurements will be assessed in a semisupine position with a completely automated device. Manual techniques will be used only if an automated device is not available. The correct size of the blood pressure cuff and correct positioning of the participant's arm are essential to the accuracy of the blood pressure measurement.
- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BR <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.

8.3.3 Electrocardiograms

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. 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 clinical studies with lenvatinib. Monitor electrocardiograms every cycle (as specified in the Schedule of Assessments) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking medications 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 echocardiogram will be performed to assess left ventricular ejection fraction (LVEF) as designated in the SoA (Section 1.3). MUGA or echocardiogram 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 upon institutional reports.

8.3.5 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

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

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

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Laboratory Manual. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

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

8.3.5.1 CBC With Differential and Clinical Chemistry

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 Test

Pregnancy testing (urine or serum) should be conducted according to Section 1.3 (SoA) and at the end of relevant systemic exposure for all arms.

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

- Pregnancy testing (urine or serum) should be conducted at monthly intervals during intervention.

- Pregnancy testing (urine or serum) should be conducted for the time it takes to eliminate systemic exposure after the last dose of study intervention(s) as noted in Section 5.1, ie, 120 days following cessation of pembrolizumab, 30 days following cessation of lenvatinib, or 180 days following cessation of chemotherapy.

- 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.

Refer to Appendix 7 for country-specific requirements.

8.3.7 Eastern Cooperative Oncology Group Performance Scale

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc.) with Grades 0 to 5. The investigator or qualified designee will assess ECOG performance 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) [ECOG-ACRIN Cancer Research Group 2016].

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 randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention randomization through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sec. 5.1 and 8.3.6, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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 he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Table 10 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**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
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in). Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse 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. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. 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 SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

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

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

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5. Lenvatinib overdose without an associated adverse event is not considered an ECI.

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

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

Arm A:

- Pembrolizumab: any dose above the protocol-prescribed dose.

- Lenvatinib: any dose above the protocol-prescribed dose if associated with an adverse event

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.”

Arm B:

Treatment of overdose with regorafenib or TAS-102 should follow the prescribing information in their respective package inserts.

In the event of overdose for any study treatment, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants except for participants enrolled in China which will be dependent on approval by the Human Genetic Resources Administration of China as specified in the SoA:

- Blood for Genetic Analysis
- Blood for RNA Analysis
- Blood for Serum Biomarker Analysis
- Blood for ctDNA Analysis
- Archival or Newly Obtained Tissue Collection

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

Refer to Appendix 7 for country-specific requirements.

8.8.1 Planned Genetic Analysis Sample Collection

Samples are to be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/IEC does not approve) sample collection for these purposes, then such samples are not to be collected at the corresponding sites. Biomarker sample collection for participants enrolled in China will be dependent on approval by the Human Genetic Resources Administration of China (HGRAC).

8.9 Future Biomedical Research Sample Collection

Not applicable

8.10 Medical Resource Utilization and Health Economics

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

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

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

8.11 Visit Requirements

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

8.11.1 Screening

Documented informed consent must be provided prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study intervention unless otherwise indicated in the SoA (Section 1.3).

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 Treatment Period

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

8.11.2.1 Telephone Contact Visit

Telephone contact or visit on Cycle 1 Day 8 will be conducted to assess participants for development of early toxicity as outlined in the SoA (Section 1.3). At the C1D8 telephone visit and if required between clinic visits, participants will have BP 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 Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP retest, or other clinically appropriate intervention(s).

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study treatment due to disease recurrence or start of a new anticancer therapy will move into Safety Follow-up and then proceed directly to Survival Follow-up as described in Section 8.11.4.3.

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. Additional details regarding participant treatment discontinuation can be found in Section 7.1.

8.11.4 Posttreatment Visits

8.11.4.1 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 the initiation of a new anticancer treatment, whichever comes first. If a participant has a discontinuation visit ≥30 days after the last dose of study intervention, the Safety Follow-up Visit is not required.

8.11.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up. Follow-up visits after treatment discontinuation must coincide with the imaging schedule until disease progression, death, or end of study. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Every effort must be made to collect imaging until the start of new anticancer therapy, confirmed PD, or death. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

8.11.4.3 Subsequent Anti-neoplastic Therapy

Details of subsequent therapies for cancer and/or details of radiation therapy and surgery for the treatment of the cancer, after discontinuation of study intervention, will be collected. Reasons for starting subsequent anti-neoplastic therapies including access to other PD-1/PD-L1 inhibitors, or investigational drugs will be collected.

8.11.4.4 Survival Follow-up Contacts

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.

8.11.5 Survival Status

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, 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 E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will be included in the sSAP.

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

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3 randomized study of lenvatinib in combination with pembrolizumab versus standard of care in participants with metastatic colorectal cancer who have received and progressed on or after or became intolerant to prior treatment
Treatment Assignment	Approximately 434 participants will be randomized in a 1:1 ratio between two treatment groups: (1) the lenvatinib plus pembrolizumab arm and (2) the SOC arm. Stratification factor is: Presence of liver metastasis (Yes/No). This is an open-label study.
Analysis Populations	Efficacy: ITT Safety: APaT Patient-reported outcome: FAS
Primary Endpoint(s)	Overall survival
Key Secondary Endpoints	Progression-free survival per RECIST 1.1 as assessed by BICR. Objective response rate per RECIST 1.1 as assessed by BICR.
Statistical Methods for Key Efficacy Analyses	The primary hypothesis testing for OS and secondary hypothesis testing for PFS 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 [Miettinen, O. 1985].
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the M&N method.

Interim Analyses	**Efficacy** One interim analysis is planned in this study. Results will be reviewed by an eDMC. CCI [redacted] CCI [redacted] **Safety** An interim safety analysis will be performed and reviewed by the eDMC 6 months after first participant is randomized. Afterwards, the eDMC will review safety data periodically in the study. Details will be specified in the DMC charter.
Multiplicity	The overall type I error over the primary and secondary hypotheses is strongly controlled at 2.5% (1-sided), with 2.5% initially allocated to OS (H1), 0% to PFS (H2), and 0% to ORR (H3). By using the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013], if one hypothesis is rejected, the alpha will be shifted to other hypotheses.
Sample Size and Power	The planned sample size is approximately 434 participants. It is estimated that there will be ~ 336 OS events at the final analysis. With 336 OS events, the study has 90% power for detecting a HR of 0.7 at an initially assigned 0.025 (1-sided) significance level.
Abbreviations: APaT = all participants as treated; BICR = blinded independent central review; CI = confidence interval; DMC = data monitoring committee; eDMC = external data monitoring committee; FAS = full-analysis set; HR = hazard ratio; ITT = intent to treat; M&N = Miettinen and Nurminen; ORR = objective response rate; OS = overall survival; PFS = progression free survival; SOC = standard of care	

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.

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

This study is being conducted as a randomized, open-label study, i.e., participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned. Although the study is open label, analyses or summaries generated by randomized intervention assignment, or actual intervention received will be limited and documented.

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

Primary

- **Overall Survival**

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

Secondary

- **Progression-free survival**

  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.

- **Objective Response Rate**

  The ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

- **Duration of Response**

  For participants who demonstrate confirmed CR or PR, duration of response is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, SAEs, fatal AEs, laboratory tests, and vital signs. Furthermore, specific events will be collected and designated as ECIs as described in Section 8.4.7.

9.4.3 PRO Endpoints

- Change from baseline in EORTC QLQ-C30 global health status/QoL, physical functioning and appetite loss and EORTC QLQ-CR29 bloating scores for the combination of lenvatinib plus pembrolizumab versus SOC

- Time to deterioration in EORTC QLQ-C30 global health status/QoL, physical functioning and appetite loss and EORTC QLQ-CR29 bloating scores for the combination of lenvatinib plus pembrolizumab versus SOC

- Change from baseline in EQ-5D VAS for the combination of lenvatinib plus pembrolizumab versus SOC

Additional details of the PRO endpoints, including analyses of the remaining functioning and symptom scores of the EORTC QLQ-C30 and EORTC QLQ-CR29 and VAS of the EQ-5D-5L, will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the primary population for the analysis of efficacy data in this study. The ITT population consists of all randomized participants. Participants will be analyzed in the treatment arm to which they are randomized. Details of the approach to handling missing data are provided in Section 9.6.1.4.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

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

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.

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 may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

9.6.1 Statistical Methods for Efficacy Analyses

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

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 [Miettinen, O. 1985].

9.6.1.1 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curve**s**. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified 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 date the participant was last known to be alive.

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 arms. The HR and its 95% CI from the stratified 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.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the 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 a PD event.

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In order 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 anti-cancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than complete response, 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 the primary and sensitivity analyses are summarized in Table 11.

Table 11 CCI

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Abbreviations: PD = progressive disease

9.6.1.3 Objective Response Rate

The stratified M&N method will be used for the comparison of ORR between 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. The stratification factors used for randomization (see 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 (1934) [Clopper, C. J. and Pearson, E. S. 1934].

9.6.1.4 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 12.

Table 12 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population
Primary Analyses		
OS	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT
Key Secondary Analyses		
PFS per RECIST 1.1 by BICR	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT
ORR per RECIST 1.1 by BICR	Testing and estimation: stratified Miettinen and Nurminen method	ITT

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Abbreviations: BICR = blinded independent central review; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.

Details about DOR evaluation will be provided in the sSAP.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 13). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol. Adverse events that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program, and determination of statistical significance is not expected to add value to the safety evaluation. The combination of lenvatinib plus pembrolizumab has not been found to be associated with any new safety signals. Finally, there are no known AEs associated with participants with CRC for which determination of a p-value is expected to impact the safety assessment.

Tier 2 Events

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

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
Tier 3	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 due to AE		X
	Death		X
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)		X
	Change from Baseline Results (lab toxicity shift, vital signs)		X
Abbreviations: AE = adverse events; SOC = standard of care			

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

This section describes the planned analyses for the PRO endpoints.

Change from Baseline

The time point for the change from baseline will be determined based on blinded data review prior to the database lock for any PRO analysis and documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the global health status/QoL, physical, appetite loss and bloating, a constrained longitudinal data analysis

model proposed by Liang and Zeger [Liang, Kung-Yee and Zeger, Scott L. 2000] will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction, and the stratification factors used for randomization (see Section 6.3.2) as covariates. The treatment difference in terms of least square mean change from baseline will be estimated from this model together with 95% CI. Model-based least square mean with 95% CI will be provided by treatment group for PRO scores at baseline and postbaseline time point.

Time-to-Deterioration

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

Details of PRO analyses will be described in the sSAP.

9.6.4 Demographic and Baseline Characteristics

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

The eDMC will serve as the primary reviewer of the results of the IAs and will make recommendations for discontinuation of the study or modification to the executive oversight committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee and potentially other limited Sponsor personnel may be unblinded to the treatment level results in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of IAs will be documented by the unblinded statistician. Additional logistic details will be provided in the eDMC Charter.

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

9.7.1 Efficacy Interim Analysis

One IA is planned in addition to the FA for this study. For the IA and FAs, all randomized participants will be included. Results of the IAs will be reviewed by the eDMC. Details of the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 9.8.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 14.

Table 14 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA	OS (PFS and ORR if OS is rejected)	Both ~260 OS events have been observed and ~ 7 months after last participant randomized	~ 18 months	• Interim OS analysis • Final PFS and ORR analysis
FA	OS	both ~336 OS events have been observed and ~ 7 months after interim analysis	~ 25 months	• Final OS analysis
Abbreviations: FA = final analysis; IA = interim analysis; ORR = objective response rate; OS = overall survival; PFS = progression free survival.				

9.7.2 Safety Interim Analysis

The eDMC will be responsible for periodic interim safety reviews as specified in the eDMC charter. An interim safety analysis will be performed 6 months since first participant is randomized. Afterwards, the eDMC will review safety data periodically in the study. Interim safety analyses will also be performed at the time of interim efficacy analyses. Details will be specified in the eDMC charter.

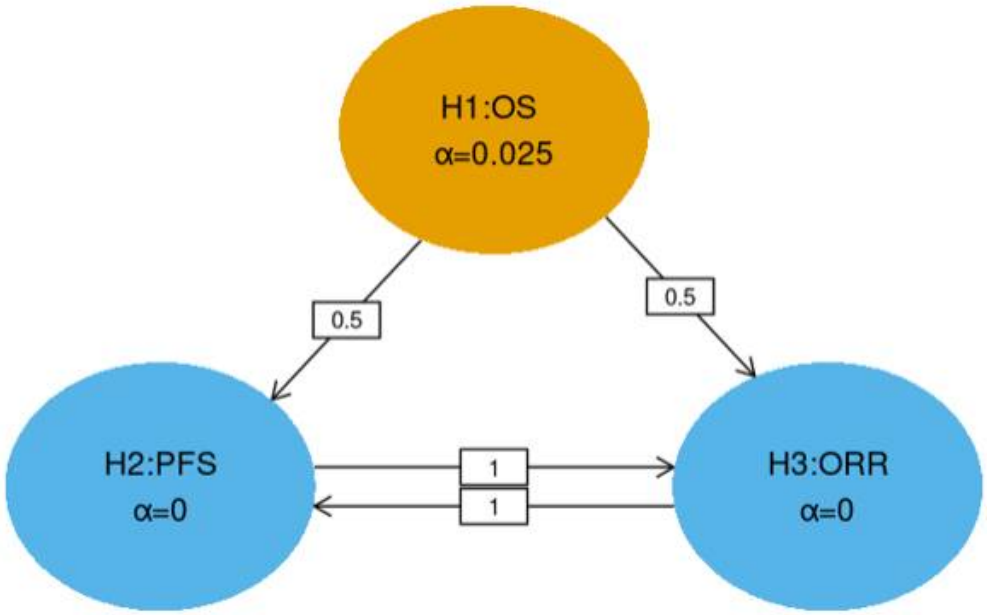
9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Note that if the OS null hypothesis is rejected at FA of the study, the previously computed PFS and ORR test statistics at IA may be used for inferential testing with its updated bounds considering the α reallocation from the OS hypothesis. Figure 3 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the

hypothesis. The weights for reallocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses.

The initial α assigned to OS, PFS and ORR will be 0.025, 0 and 0, respectively. If OS hypothesis is rejected, the corresponding alpha can be reallocated equally to PFS and ORR. If the PFS hypothesis is rejected, the corresponding alpha can be reallocated to ORR. If the ORR hypothesis is rejected, the corresponding α can be reallocated to PFS.

Figure 3 Multiplicity Diagram for Type I Error Control



Abbreviations: ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
Note: If OS null hypothesis is rejected, the allocation strategy allows testing of PFS and ORR at α = 0.0125, separately.

9.8.1 Overall Survival

The study will test OS at IA and FA. Following the multiplicity strategy as outlined in Figure 3, the OS hypothesis will be tested at α=0.025. Table 15 shows the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds.

Table 15 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	**Value**	**α=0.025**
IA: 77%* N: 434 Events: 260 Month: 18	Z	2.2976
	p (1-sided)[a]	0.0108
	HR at bound[b]	0.7517
	P(Cross) if HR=1[c]	0.0108
	P(Cross) if HR=0.7[d]	0.7185
FA N: 434 Events: 336 Month: 25	Z	2.0177
	p (1-sided)[a]	0.0218
	HR at bound[b]	0.8022
	P(Cross) if HR=1[c]	0.0250
	P(Cross) if HR=0.7[d]	0.9000

Abbreviations: HR = hazard ratio; IA = interim analysis, FA = final analysis.
The number of events and timings are estimated.
*Percentage of total planned events at the interim analysis.
[a]*p* (1-sided) is the nominal α for group sequential testing.
[b]HR at bound is the approximate HR required to reach an efficacy bound.
[c]P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d]P(Cross if HR=0.7) is the probability of crossing a bound under the alternative hypothesis.

The bounds provided in the table above are based on the assumptions that the expected number of events at IA and FA are 260 and 336, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an IA and leave reasonable α for the FA, the minimum α spending strategy will be adopted. At an 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 number of 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 exceeds 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.

The final analysis will use the remaining Type I error that has not been spent at the earlier analyses. The observed event counts for all analyses will be used to compute correlations.

9.8.2 Progression-free Survival

The study will test PFS at IA only if the OS null hypothesis is rejected. Following the multiplicity strategy as outlined in Figure 3, the PFS hypothesis may be tested at α=0.0125 (if the OS null hypothesis is rejected, but not the ORR hypothesis) or at α= 0.025 (if both the OS and ORR null hypothesis is rejected). Table 16 shows the boundary properties for each of these α levels for the PFS analysis. Note that the final row indicates the total power to reject the null hypothesis for PFS at each α level.

Table 16 Efficacy Boundaries and Properties for Progression-Free Survival Analyses

Analysis	Value	α=0.0125	α=0.025
IA N = 434 Events*: 404 Month: 18	Z	2.2414	1.9600
	p (1-sided) [a]	0.0125	0.025
	HR at bound[b]	0.8000	0.8227
	P(Cross) if HR=1[c]	0.0125	0.025
	P(Cross) if HR=0.65[d]	0.9820	0.9912

Abbreviations: HR = hazard ratio; IA = interim analysis.
The number of events and timing is estimated.
[a]*p* (1-sided) is the nominal α for group sequential testing.
[b]HR at bound is the approximate HR required to reach an efficacy bound.
[c]P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d]P(Cross if HR=0.65) is the probability of crossing a bound under the alternative hypothesis.

9.8.3 Objective Response Rate

The study will test ORR only once at the IA if the OS null hypothesis is rejected. Following the multiplicity strategy as outlined in Figure 3, the ORR hypothesis may be tested at α=0.0125 (if the OS null hypothesis is rejected, but not the PFS hypothesis) or at α= 0.025 (if both the OS and PFS null hypothesis is rejected). Power at the possible α-levels as well as the approximate treatment difference required to reach the bound (ΔORR) are shown in Table 17, assuming underlying 2% and 12% response rates in the control and experimental groups, respectively.

Table 17 Possible α Levels and Approximate ORR Difference Required to Demonstrate Efficacy for Objective Response at IA

α	~Δ Objective Response Rate (ORR)	Power (ΔORR=0.1)
0.0125	0.0549	0.970
0.025	0.0480	0.985

9.8.4 Safety Analysis

The eDMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. eDMC 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 ORR, PFS, and OS adopting a conservative multiplicity adjustment will be prespecified in the sSAP.

9.9 Sample Size and Power Calculations

The study will randomize 434 participants in a 1:1 ratio into the lenvatinib plus pembrolizumab arm the SOC arms. OS are primary endpoint for the study, with PFS and ORR as the key secondary endpoints.

For the OS endpoint, based on a target number of 336 events and 1 IA at approximately 77% of the target number of events, the study has approximately 90% power to detect a HR of 0.7 at the initially allocated α=0.025 (1-sided).

For the PFS endpoint, based on a target number of 404 events at the IA (final PFS analysis), the study has approximately 98.2% power to detect a HR of 0.65 at the reallocated α=0.0125 (1-sided) if OS hypothesis is rejected.

Based on the 434 participants with at least 7 months of follow-up, the power of the ORR testing at the reallocated α=0.0125 (1-sided) if OS hypothesis rejected is approximately 97.0% to detect a 10-percentage point difference between an underlying 2% ORR in the control arm and a 12% ORR in the experimental arm.

Note that the above power calculations are based on a constant HR assumption.

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9.10 Subgroup Analyses

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

- Geographic region (Asia vs. Western Europe/North America vs. Rest of World)
- ECOG performance status (0, 1)
- Age category (<65 years, ≥65 years)
- Sex (female, male)
- Race (white, all others)
- Presence of liver metastasis (Yes, No)
- BRAF (wild type, mutant)
- RAS (wild type, mutant)
- Investigators' choice of standard of care chemotherapy prior to randomization (Regorafenib versus TAS102)

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 ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot. The subgroup analyses for OS will be conducted using an unstratified Cox model.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of Exposure for a participant is defined as the number of cycles and number of days for which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the overall study intervention, and for lenvatinib and pembrolizumab separately, 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)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. 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 his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 External Data Monitoring Committee

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

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

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

10.1.4.2 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

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 trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will

review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 Compliance with Law, Audit, and 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.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator

or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 18 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 18 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV[a] MCH[a] %Reticulocytes[a]	WBC count with Differential[b] Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN[c]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	Carbon dioxide (CO_2 or Bicarbonate[a])	Chloride	Phosphorus
	Creatinine[d]	Sodium	ALT/SGPT	Total Protein
	Glucose nonfasting	Calcium	Alkaline phosphatase	Magnesium
	Amylase/Lipase[e]		LDH	
Routine Urinalysis[f]	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)[g]			
Other Screening Tests	• PT/INR and aPTT/PTT[h] • FSH (as needed in WONCBP only)[i] • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) NOTE: certain ex-US sites require testing for HIV and hepatitis B and C during screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable[j]. • Thyroid panel: TSH, T3/FT3, and T4/FT4[k]			

Laboratory Assessments	Parameters
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential a. Performed only if considered local standard of care. b. Absolute or % acceptable per institutional standard. c. Urea is acceptable if BUN is not available as per institutional standard. d. Glomerular filtration rate (GFR) (measured or calculated) or creatinine clearance can be used in place of creatinine. e. Obtain lipase and amylase test for screening, EOT and 30-day follow-up. f. If urine dipstick is abnormal, urinalysis must be performed. g. Pregnancy tests must be repeated before every cycle. Perform on WOCBP only 24 hours before first dose. h. Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulants. i. If necessary, to check menopausal status. j. HBsAg or HBV DNA. HCV RNA (qualitative) or HCV antibody. k. Participants may be dosed in subsequent cycles after C1D1 while thyroid function tests are pending. Free T3/T4 is acceptable when total T3/T4 cannot be determined.	

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

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 non-therapeutic 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 (also referred to as Sponsor's product) 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 pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 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 pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

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 his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
    - Yes, there is a reasonable possibility of Sponsor's product relationship:

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

10.4 Appendix 4: Medical Device 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 following 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 1 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 two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

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

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

Not applicable

10.7 Appendix 7: Country-specific Requirements

10.7.1 Germany-specific Requirements

Women of childbearing potential at study sites in Germany must have a pregnancy test performed before the start of the study and monthly during the treatment period and for the duration of the poststudy contraception requirements.

Legally Acceptable Representative

For a participant to be eligible to participate in Germany, they must be capable of signing the informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Inclusion Criterion #11: Change for Germany: Per approved label of TAS-102, 6 months contraception is required after the treatment of TAS-102 is discontinued.

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 180 days after the last dose of TAS-102.

Exclusion Criterion #10: Only ECHO scans will be done at the German sites. No MUGA scans will be done in Germany.

Exclusion Criterion #28: HIV testing is mandatory.

Exclusion Criterion #29: Hepatitis B and C testing is mandatory.

10.7.2 Argentina-specific Requirements

Women of childbearing potential at study sites in Argentina must have a pregnancy test performed before the start of the study and monthly during the treatment period and for the duration of the poststudy contraception requirements.

Exclusion Criterion #28: HIV testing is mandatory.

Exclusion Criterion #29: Hepatitis B and Hepatitis C testing is mandatory.

10.7.3 China-specific Requirements

Section 1.3.1 Arm A: Lenvatinib Plus Pembrolizumab Treatment

Section 1.3.2 Arm B: Regorafenib Treatment

Section 1.3.3 Arm B: TAS-102 Treatment

For all 3 Arms:

- SoA Hematology and Chemistry: Lipase and Amylase testing to be assessed within 7 days prior to the first dose of the study intervention.
- SoA Urine dipstick: Testing to be assessed within 7 days prior to the first dose of the study intervention.
- Participants with ≥2+ proteinuria on urine dipstick during screening will undergo 24-hour urine collection for quantitative assessment of proteinuria.
- Biomarker sample collection for participants enrolled in China will be dependent on approval by the Human Genetic Resources Administration of China:
- Biomarker Section
    - Blood for Genetic Analysis
    - Blood for RNA Analysis
    - Blood for Serum Biomarker Analysis
    - Blood for ctDNA Analysis
    - Archival or Newly Obtained Tissue Collection

Section 5.1 Inclusion Criteria

- Inclusion Criterion #4: For study sites in China, tissue sample collected at screening for MSI-H/dMMR central retrospective analysis is required, to support possible future requirement from health authority.

Section 8.8 Biomarkers

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

10.7.4 Korea-specific Requirements

General: All drugs marketed in Korea must follow the product label with regard to inclusion criteria requirements. If the product label has more stringent requirements than the protocol, the more stringent requirement must be followed.

Concerning "previous standard treatment" in Inclusion Criterion #2:

The drug labeling in Korea for drugs listed below (a-d) presented as the previous standard treatment described in the inclusion criterion above are as follows:

a. Fluoropyrimidine, irinotecan and oxaliplatin.

1) Fluoropyrimidine - Capecitabine is referred

- Colorectal cancer

  - Metastatic colorectal cancer

  - Adjuvant treatment after surgery for Stage III (Dukes' C) colon cancer

    ✓ Used alone when fluoropyrimidine treatment is the first choice following complete surgical resection of the primary tumor in a participant with Stage III (Dukes'C) colon cancer

    ✓ Used in combination with oxaliplatin following complete resection of the primary tumor

2) Irinotecan

- Relapsed, advanced metastatic rectal or colon cancer after fluorouracil treatment

- Combined with fluorouracil and calcium polynate in advanced rectal cancer or colon cancer participants without neoadjuvant therapy

3) Oxaliplatin

- Combined with 5-fluorouracil and folinic acid (leucovorin) as a first-line treatment for metastatic colon and rectal cancer

- Used as adjuvant treatment in combination with 5-fluorouracil and folinic acid (leucovorin) for Stage III (Duke's C) colon cancer after complete surgical resection of the primary tumor

b. With or without an anti-VEGF monoclonal antibody (bevacizumab)

Metastatic colorectal cancer - treated in combination with fluoropyrimidine-based chemotherapy. Combined with chemotherapy based on fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin if it is planned to use this drug as a second-line therapy in a participant with advanced metastatic colorectal cancer after chemotherapy containing this drug as a first-line therapy.

c. With anti-EGFR mAbs (cetuximab or panitumumab) for RAS (KRAS/NRAS) WT participants.

1) Cetuximab

- In an EGFR-positive, RAS wild-type metastatic colorectal cancer participant.
- Combined with irinotecan-based chemotherapy
- First-line therapy in combination with FOLFOX
- Used alone in a participant who is intolerant to irinotecan and have failed the therapy including oxaliplatin and irinotecan

2) Panitumumab – Not approved in Korea

d. BRAF inhibitor (in combination with cetuximab +/- binimetinib) for BRAF V600E mutated mCRC.

1) BRAF inhibitor – Not approved in Korea

Section 5.1 Inclusion Criterion # 11: Per approved label of TAS-102, 6 months contraception is required after the treatment of TAS-102 is discontinued.

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 180 days after the last dose of TAS-102.

According to local label of regorafenib, the following test should be performed:

- Coagulation parameter monitoring is required for participants with conditions predisposing to bleeding, and in those treated with anticoagulants (eg, warfarin and phenprocoumon) or other concomitant medicines that increase the risk of bleeding.
- For participants with hepatic impairment, a hepatic function test (ALT, AST, bilirubin) should be performed before first administration and monitored at least every 2 weeks for 2 months from first administration.

10.7.5 Spain-specific Requirements

Women of childbearing potential at study sites in Spain must have a pregnancy test performed before the start of the study and monthly during the treatment period and for the duration of the poststudy contraception requirements.

10.7.6 UK-specific Requirements

Section 5.1 Inclusion Criterion # 11: Per approved label of TAS-102, 6 months contraception is required after the treatment of TAS-102 is discontinued.

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 180 days after the last dose of TAS-102.

Section 5.1 Inclusion Criterion #12 and Appendix 5 Contraception Guidance

If the highly effective contraception that a WOCBP uses relies on hormones, then a barrier contraception must also be used.

Section 6.5.1.1 Arm A Prohibited Concomitant Medication(s)

Live or live-attenuated vaccines within 30 days before first dose of study intervention, while participating in the study and 120 days after last dose of pembrolizumab. Note: Killed vaccines are allowed.

10.7.7 Canada-specific Requirements

Section 6.6.2.9 Lenvatinib should be discontinued in any participant who develops gastrointestinal perforation of any grade or ≥Grade 3 fistula.

Update to Section 5.1 Inclusion Criterion # 11: Per approved label of TAS-102, 6 months contraception is required after the treatment of TAS-102 is discontinued.

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 180 days after the last dose of TAS-102.

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

Not applicable.

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
3L	third-line
ADA	anti-drug antibodies
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
anti-PD-L1	anti-PD1 antibody
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BICR	blinded independent central review
BID	twice daily
BMI	body mass index
BP	blood pressure
BRAF	gene that encodes the B-Raf protein
BSA	Body Surface Area
BUN	blood urea nitrogen
C	cycle
C30	cancer-specific 30 items
CD28	cluster of differentiation 28
CD3	cluster of differentiation 3
CD3ζ	CD3 zeta
CD8+	cluster of differentiation 8 – cytotoxic T cell
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CR29	colorectal cancer-specific 29 items
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CT26	N-nitroso-N-methylurethane induced, undifferentiated colon carcinoma cell line
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein 4

Abbreviation	Expanded Term
CYP3A4	Cytochrome P450 3A4
DCR	disease control rate
DDI	drug-drug interaction
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
eDMC	external data monitoring committee
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	end of intervention
EORTC	European Organization for Research and Treatment of Cancer
EOT	end of treatment
ePRO	Electronic patient reported outcome
ePROs	electronic patient-reported outcomes
EQ-5D	EuroQoL-5D
EQ-5D-5L	5-dimension Questionnaire
E-R	exposure response
EuroQoL	European Quality of Life
ESMO	European Society for Medical Oncology
FA	final analysis
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FGF	fibroblast growth factor
FGFR1	fibroblast growth factor receptor 1
FLT	vascular endothelial growth factor receptor 1
FLT4	vascular endothelial growth factor receptor 2
FOLFIRI	5-fluorouracil, leucovorin and irinotecan
FOLFOX	5-fluorouracil, leucovorin and oxaliplatin
FoxP3+	forkhead box P3
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate

Abbreviation	Expanded Term
GI	gastrointestinal
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination deficiency
HRT	Hormone replacement therapy
HRQoL	health-related quality of life
HUVEC	human umbilical vein endothelial cell
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	Independent Central Review
iCR	iRECIST complete response
iCRO	imaging CRO
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
INR	international normalized ratio
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITT	intention-to-treat
IV	intravenous
IUO	Investigational Use Only
IVD	in vitro diagnostic
JSCCR	Japanese Society for Cancer of the Colon and Rectum
KDR	kinase Insert Domain Receptor
KIT	receptor tyrosine kinase protein
KRAS	KRAS Proto-Oncogene, GTPase
LVEF	left ventricular ejection fraction
M&N	Miettinen and Nurminen
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
mCRC	metastatic colon cancer
MEK	Mitogen-activated Protein Kinase

Abbreviation	Expanded Term
MMR	Mismatch repair
MMRd	mismatch repair deficiency
MMRp	mismatch repair protein
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
mTOR-S6K-S6	mammalian target of rapamycin - ribosomal S6 kinase
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	non investigational medicinal product
NR	not reached
NRAS	neuroblastoma ras viral oncogene homolog
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ONJ	Osteonecrosis of the jaw
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell-death 1
PDGFRα	Platelet-derived growth factor receptor alpha
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression free survival
P-gp	P-gylcoprotein
PK	pharmacokinetic
PKCθ	protein kinase C-theta
pMMR	proficient mismatch repair
po	orally
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	patient-reported outcome
PT	prothrombin time
QXW	every X weeks
QD	daily
QLQ	quality of life questionnaire
QLQ-C30	Quality of Life Questionnaire Core 30 items
QoL	quality of life

Abbreviation	Expanded Term
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RAG	Recombination Activating Gene
RAS	gene that makes a protein called KRAS
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RET	rearranged during transfection
RNA	ribonucleic acid
RP2D	recommended dose Phase 2 dose
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
RR	respiratory rate
RTK	receptor tyrosine kinase
RTKi	receptor tyrosine kinase inhibitor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SHP-1	Src homology region 2 domain-containing phosphatase-1
SHP-2	Src homology region 2 domain-containing phosphatase-2
SIM	Site Imaging Manual
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TAM	tumor associated macrophages
TAS	trifluridine and tipiracil hydrochloride
TB	Tuberculosis
TBL	total bilirubin
TEA	treatment eligibility assessment
TIDM	Type 1 diabetes mellitus
TIL	tumor-infiltrating lymphocyte
TMB	Tumor mutational burden
Tregs	regulatory T cells
TSH	Thyroid stimulating hormone
TTD	time to deterioration
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US	United States
VAS	Visual Analogue Scale
VEGF	vascular endothelial growth factor
VEGFR1	vascular endothelial growth factor receptor 1
VEGFR2	vascular endothelial growth factor receptor 2
VEGFR3	vascular endothelial growth factor receptor 3

Abbreviation	Expanded Term
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	women of nonchildbearing potential
WT	wild type
ZAP70	zeta-chain-associated protein kinase

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