Official Protocol Title:	A Multicenter, Open-label Phase 2 Study of Lenvatinib (E7080/MK-7902) Plus Pembrolizumab (MK-3475) in Previously Treated Subjects with Selected Solid Tumors (LEAP-005)
NCT number:	NCT03797326
Document Date:	18-Jan-2024

Title Page

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Protocol Title: A Multicenter, Open-label Phase 2 Study of Lenvatinib (E7080/MK-7902) Plus Pembrolizumab (MK-3475) in Previously Treated Subjects with Selected Solid Tumors (LEAP-005)

Protocol Number: MK-7902-005-06 (E7080-G000-224)

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 cofunded by MSD and Eisai.

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	140,509
Eudra CT Number	2018-003747-37

Approval Date: 18 January 2024

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 6	18-JAN-2024	This change provides an option for participants to continue in an extension study
Amendment 5	14-OCT-2022	Sponsor underwent an entity name change and update to the address
Amendment 4	11-JUN-2021	Amended to indicate that the triple-negative breast cancer (TNBC) and the ovarian cancer cohort will not enroll participants in the expansion phase and to correct minor errors
Amendment 3	10-DEC-2020	Amended to add lenvatinib monotherapy arms to the ovarian and colorectal cancer (CRC) cohorts to obtain contribution of component data and to add a pancreatic cancer cohort
Amendment 2	17-JUN-2020	Amended to update and clarify language for progression of the study to the expansion phase and to correct minor errors
Amendment 1	12-JUN-2019	Amended to incorporate changes requested by Health Authorities and correct minor errors
Original protocol	25-OCT-2018	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendment:

This change provides an option for participants to continue in an extension study.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 6.7, Intervention After the End of the Study	Updated language to provide guidance for eligible participants to continue in an extension study, if available.	This change provides an option for participants to continue in an extension study.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1, Synopsis	Estimated Duration of Study: Updated the number of months.	To align with the revised estimate for study duration.
Section 1.1, Synopsis	Duration of Participation: Updated language to include participation in an extension study.	The language updates align with the enrollment of eligible participants to an extension study.
4.4, Beginning and End of Study Definition	The language was updated to include participation in an extension study.	Refer to Section 1.1 duration of participation rationale.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Updated language specific to participants who enter the extension study.	To provide safety reporting directions for participants who enter the extension study.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multicenter, Open-label Phase 2 Study of Lenvatinib (E7080/MK-7902) Plus Pembrolizumab (MK-3475) in Previously Treated Subjects with Selected Solid Tumors (LEAP-005)

Short Title: Pembrolizumab plus lenvatinib as second-line plus intervention for select solid tumors

Acronym: Protocol 005

Hypotheses, Objectives, and Endpoints:

In participants with triple-negative breast cancer (TNBC, Cohort A), ovarian cancer (Cohort B), gastric cancer (Cohort C), colorectal cancer (CRC, Cohort D), glioblastoma (GBM, Cohort E), biliary tract cancers (BTC, Cohort F), or pancreatic cancer (Cohort G), the objectives and endpoints outlined below will be evaluated.

Efficacy analyses will be performed by cohort/tumor type and Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ (Section 4.2.3.1), will be used for all tumor cohorts except GBM, which will use Response Assessment in Neuro-Oncology (RANO) Criteria (Section 4.2.3.1.3).

For Cohorts A-F, RECIST 1.1 (RANO for GBM) by investigator assessments will be used in the initial 30 enrolled participants. RECIST 1.1 (RANO for GBM) by blinded independent central review (BICR) will be used in cohorts that expand to combine the initial 30 enrolled participants with the additional 70 to 100 expansion participants. For Cohort G, which will enroll 100 participants, RECIST 1.1 by BICR will be used.

For participants receiving pembrolizumab (Arm 1 only), modified RECIST 1.1 for immune-based therapeutics (iRECIST) will be used by investigators to assess tumor response and progression, and make treatment decisions, as well as for exploratory efficacy analyses (Section 4.2.3.1.2).

Primary Objectives	Primary Endpoints
Objective: To evaluate objective response rate (ORR) of pembrolizumab in combination with lenvatinib per tumor cohort based on RECIST 1.1 by investigator assessments in initial cohorts and BICR in cohorts that expand combining the initial and expansion cohorts (Cohorts A-F). In Cohort G, RECIST 1.1 by BICR will be utilized in all participants. (For participants with GBM, response will be assessed based on Response Assessment in Neuro-Oncology [RANO] criteria; all further references to RECIST 1.1 assessment apply to all cohorts except GBM.)	Objective response (OR), complete response (CR), or partial response (PR)
Objective: To assess safety and tolerability of treatment with pembrolizumab in combination with lenvatinib per tumor cohort assessed by the proportion of adverse events (AEs).	AEs Discontinuation due to AEs
Objective: To assess safety and tolerability of treatment with lenvatinib monotherapy assessed by the proportion of AEs.	AEs Discontinuation due to AEs
Secondary Objectives	Secondary Endpoints
Objective: To evaluate disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) of pembrolizumab in combination with lenvatinib per tumor cohort based on RECIST 1.1 (RANO for GBM) by investigator assessments in initial cohorts and BICR in cohorts that expand combining the initial and expansion cohorts (Cohorts A-F). In Cohort G, RECIST 1.1 by BICR will be utilized in all participants.	Disease control, defined as best overall response of CR, PR, or SD DOR, determined by disease assessment defined as the time from the earliest date of qualifying response until the earliest date of disease progression or death from any cause, whichever comes first. PFS, defined as the time from the first day of study intervention to the day of the first documentation of disease progression or death from any cause, whichever occurs first.

Objective: To evaluate overall survival (OS) of pembrolizumab in combination with lenvatinib per tumor cohort.	OS, defined as the time from the first day of study intervention to day of death from any cause.
Objective: To evaluate ORR, DCR, DOR, PFS, and OS of lenvatinib monotherapy based on RECIST 1.1 by BICR.	OR DCR DOR PFS OS
Objective: To characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with pembrolizumab in participants per tumor cohort (Cohorts A-F only).	Plasma concentration of lenvatinib.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of participants with relapsed/refractory TNBC, ovarian cancer, gastric cancer, CRC, GBM, BTC, or pancreatic cancer
Population	Participants with TNBC, ovarian cancer, gastric cancer, CRC, GBM, BTC, or pancreatic cancer
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	None
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 70 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:

Initially, approximately 180 participants (30 per cohort in Cohorts A-F) will be stratified by tumor cohort and enrolled in the study as described in Section 4.1.

Expansion portion of the study: an interim analysis, based on investigator assessments of efficacy, will be conducted for each tumor-specific cohort when the last of the initial 30 participants have been followed up for approximately 6 months from study entry. Since enrollment rates will be variable for each cohort, separate interim analyses may be needed for individual or groups of cohorts. In the event of slow enrollment, IAs may take place when the majority of participants have been followed up for 6 months from study entry. After Sponsor review of the results of each IA, recommendations for expansion will be given. Cohorts A and B will not enroll participants in the expansion phase. Cohorts C, E, and F will each include 100 participants: the initial 30 participants enrolled into each cohort, plus the additional 70 participants enrolled in the expansion phase. Cohort D will include 130 participants: the initial 30 participants enrolled, plus an additional 100 participants enrolled in the expansion phase, with the last approximately 60 participants randomized 1:1 to receive pembrolizumab + lenvatinib (Arm 1) or lenvatinib monotherapy (Arm 2). Additionally, Cohort G will enroll 100 participants. The potential total number of participants in the study will be 590.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Intervention	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Arm 1	Lenvatinib	20 mg	qd	Orally	Daily	Test product
Arm 1	Pembrolizumab	200 mg	q3w	IV infusion	Day 1 of each 21-day cycle	Test product
Arm 2[a]	Lenvatinib	24 mg	qd	Orally	Daily	Test product

IV = intravenous; q3w = once every 3 weeks; qd = once per day

[a] Cohort D (CRC) only.

Total Number: 2 arms

Duration of Participation	After a screening phase of up to 28 days, each eligible participant will be assigned to receive study intervention with pembrolizumab + lenvatinib (Arm 1, Cohorts A-G) or lenvatinib monotherapy (Arm 2, Cohort D only). Participants will continue on study intervention until disease progression is radiographically documented per RECIST 1.1 or RANO criteria for participants with GBM, unacceptable toxicity, withdrawal of consent, initiation of new anticancer treatment, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, pregnancy, administrative reasons requiring cessation of treatment or death. Pembrolizumab treatment will be discontinued once the participant has received 35 administrations of pembrolizumab (approximately 2 years). Participants in Arm 1 and Arm 2 may continue treatment with lenvatinib beyond 2 years if they experience clinical benefit according to the PI, with Sponsor consultation. In addition, discontinuation of study treatment with pembrolizumab and lenvatinib may be considered for participants who have attained a confirmed CR per RECIST 1.1 (or per RANO for GBM cohort) and have been treated for at least 24 weeks, receiving at least 2 additional doses of pembrolizumab beyond the date when the initial CR is declared. Participants will be permitted to continue treatment beyond RECIST 1.1- or RANO-defined progression (Arm 1 only) as long as investigator-assessed clinical stability is observed, the participant is tolerating study intervention (Section 8.2.1.5 or Section 8.2.1.6) and after obtaining documented informed consent addendum. Treatment beyond confirmed progressive disease (PD) per iRECIST or RANO may be permitted on Sponsor consultation. After the end of treatment (EOT), each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue study intervention without documented disease progression will have posttreatment follow-up imaging for disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. All participants will be contacted (by telephone or visit) approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (unless this information is not allowed to be provided due to confidentiality). The end of the study will be the date when the last participant completes the last study-related telephone call or visit, withdraws from the study, is lost to follow-up (ie, the participant is unable to be contacted by the investigator), or is planned to be enrolled in an extension study.

Study Governance Committees:

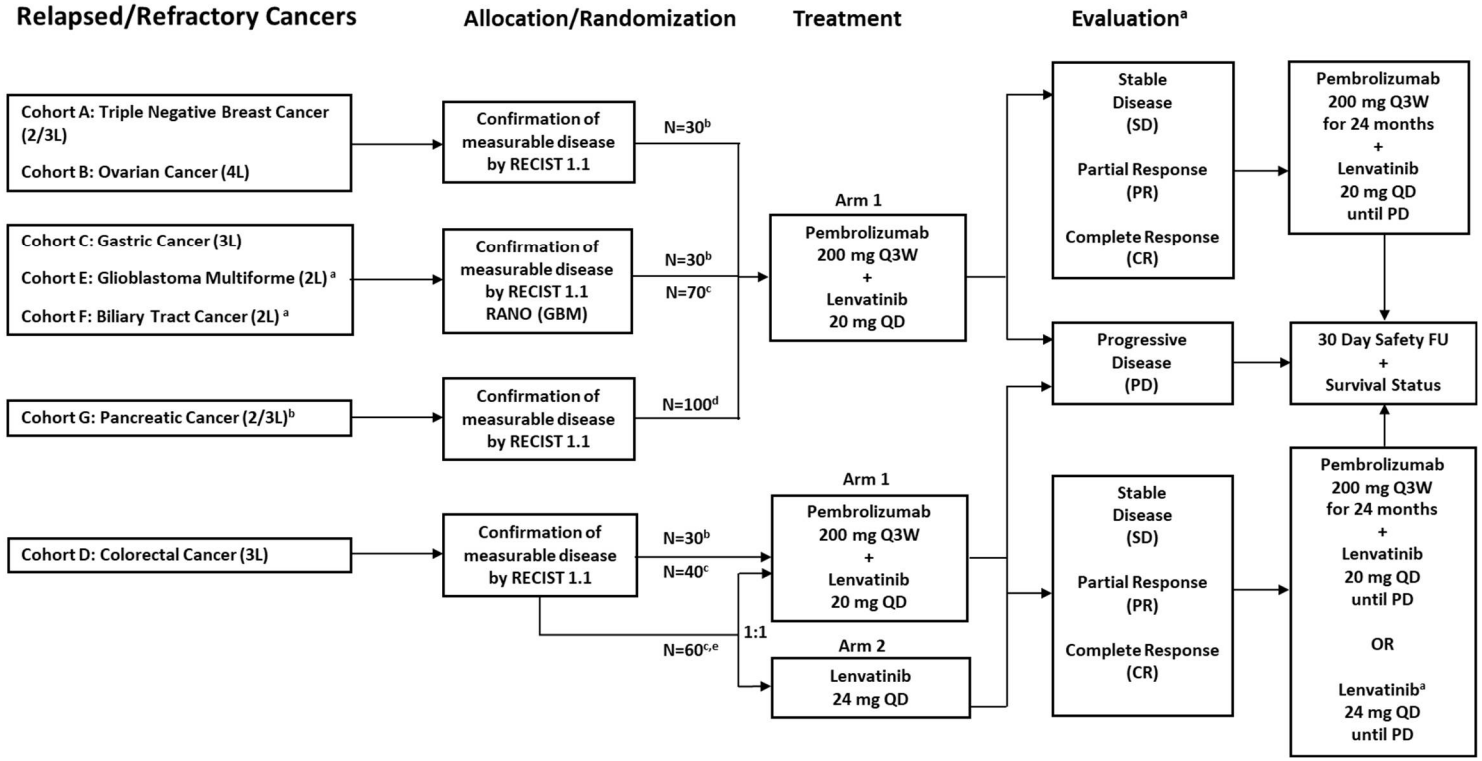
Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

Figure 1 Study Diagram



FU = follow-up; GBM = glioblastoma; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for Immune-Based Therapeutics; ORR = objective response rate; q3w = once every 3 weeks; q24w = once every 24 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RANO = Response Assessment in Neuro-Oncology; TNBC = triple-negative breast cancer.

Note: For all cohorts (except GBM), tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days) or sooner if clinically indicated, until Week 102. After Week 102, imaging should be performed q24w or sooner if clinically indicated. For participants with GBM, imaging will be performed at 6 weeks (42 days to 49 days) from the date of treatment initiation. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) until Week 18 and then every 9 weeks thereafter or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed q24w or sooner if clinically indicated.

Note: Specific cohort(s) may be terminated early and/or further enrollment stopped as noted in Section 4.1.3

[a] Evaluation of response by RECIST 1.1; RANO (GBM only); or iRECIST (Arm 1 only)

[b] Initial allocation; if adequate ORR determined, cohort expansion to 100 participants (Cohorts C, E, and F) or 130 participants (Cohort D)

[c] Expansion phase

[d] Total allocation (Cohort G)

[e] The last 60 participants will be randomized 1:1.

1.3 Schedule of Activities (SoA)

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Administrative and General Procedures												
Informed Consent	X											Consent form can be documented at any time before any protocol-specific screening procedures are performed. If the investigator plans to treat beyond disease progression, additional consent is required.
Inclusion/Exclusion Criteria	X											
Participant Identification Card	X											
Demographics	X											
Staging	X											At initial diagnosis and at study entry
Medical/Surgical History	X											

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		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.
Subsequent antineoplastic treatment									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 via telephone or email.
Allocation/randomization via IRT		X										Participants will be allocated/randomized on C1D1 (-3d) after confirmation of eligibility. All procedures and assessments on C1D1 should be performed after allocation/randomization.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Phone contact visit			X									Telephone contact or visit on C1D8 will assess participants for BP and development of early toxicity. BP will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee (See Sec. 8.3.2). The investigator or medically qualified designee (consistent with local requirements) will assess participants for development of early toxicity. An unscheduled visit can occur before C1D15 if necessary for safety.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Survival Status		←									→	Participants who experience confirmed PD or start a new anticancer therapy, will be contacted (by telephone or visit) approximately every 12 weeks to assess for survival status until death, withdrawal of consent or the end of the study, whichever occurs first (unless this information is not allowed to be provided due to confidentiality). All subsequent anticancer therapy will be recorded. Updated survival status may be requested by the Sponsor at any time during the course of the study. See Section 8.10.5.
CCI [redacted]	[redacted]											[redacted]

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
[redacted]	[redacted]											CCI [redacted]

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Administration of Study Treatment												
Pembrolizumab + lenvatinib (Arm 1) and lenvatinib monotherapy (Arm 2) Administration/Dispensing		X		X	X		X					Pembrolizumab 200 mg q3w/lenvatinib 20 mg qd (Arm 1, all cohorts); lenvatinib 24 mg qd (Arm 2, CRC cohort only); 21-day cycle. Lenvatinib will be administered 0 to 4 hours after completion of pembrolizumab administration on C1D1, C1D15, and C2D1 (Arm 1 only).
Efficacy Procedures												
Tumor Assessment - (CT/MRI)[c]	X	<---------->						X		X		All imaging visits have a scheduling window of ±7 days. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks before the EOT Visit.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Brain MRI[d]	X	<----------	----------	----------	----------	----------	---------->	X		X		All imaging visits have a scheduling window of ±7 days. For participants with GBM, brain MRI is required at baseline and every imaging visit thereafter. For non-GBM cohorts, participants with previously treated brain metastases are required to have a brain MRI at screening and at all subsequent tumor assessment time points. A brain MRI is also required for all participants when clinically indicated. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks before the EOT Visit.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Bone Scan	X	<----------					---------->	X		X		For breast cancer cohort, bone scan is required at screening. If bone metastases are present, bone scans are required every 27 weeks, or more often if clinically indicated. If CR is suspected based on anatomic imaging, a bone scan is required to confirm clearance of bone metastases either within the same imaging visit as the anatomic imaging, or on the next anatomic scan. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks before the EOT Visit.
Clinical Procedures or Assessments												
Full physical examination	X											To be performed within 7 days before the start of study treatment. Includes oral examination.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Directed Physical Examination		X			X		X		X			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. Includes oral examination.
Vital Signs (resting BP, HR, RR, and temperature), height and weight	X	X		X	X	X	X	X	X			BP and HR will be measured after the participant has been resting for 5 minutes. Height measured at screening only.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
12-lead ECG	X	X			X		X	X	X			ECG at screening, C1D1, C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. On C1D1 and C2D1: A predose ECG and a repeat ECG (approximately 2 hours after lenvatinib dosing) must be performed. For high-risk participants (as defined in Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.
MUGA or ECHO for LVEF assessment	X							X				Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study.
NYHA	X											See Appendix 6

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
ECOG performance status	X				X		X		X			To be assessed within 3 days before allocation/randomization. Should be assessed before dosing at treatment visits.
Child-Pugh Score	X											For BTC cohort only: To be assessed within 7 days of treatment initiation. Child-Pugh Score must be 5-6 (Class A) for participant eligibility.
AE monitoring	X	X	X	X	X	X	X	X	X			AEs monitored up to 30 days after last dose. SAEs monitored up to 90 days and 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	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Local Laboratory Procedures and Assessments[e]												
Hematology and chemistry laboratory assessment	X			X	X		X	X	X			Performed locally within 7 days before start of treatment. Every effort should be made to collect samples at the same time of day. LDH is only required at screening.
Urine dipstick testing	X			X	X	X	X	X	X			Performed locally within 7 days before the start of treatment. Urinalysis may be used if the use of urine dipsticks is not feasible. Participants with >1+ (30 mg/dL) 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.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
PT or INR, aPTT and Fibrinogen	X											Screening samples collected within 7 days of treatment initiation. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
T3, FT4, TSH	X				X			X	X			At Screening, C2D1, **then every 2 cycles thereafter.** Screening samples to be collected within 7 days of treatment initiation. Free T3 is acceptable where T3 cannot be determined.
Pregnancy test (WOCBP only)	X				X		X	X	X	X		WOCBP require a negative test before randomization and within 24 hours before to the first dose of study intervention. If less than 24 hours have elapsed between the randomization test and the first dose of study intervention, another pregnancy test is not required.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
HIV, HBsAg, HCV	X											Testing is not required unless mandated by local health authority.
Pharmacokinetics/Biomarkers												
Pembrolizumab PK		X			X		X*					*Predose C1D1, C2D1, and C8D1 only; Cohorts A-F only.
Pembrolizumab antidrug antibodies		X			X		X*					*Predose C1D1, C2D1, and C8D1 only; Cohort A-F only.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Lenvatinib PK		X		X	X							C1D1: 0.5-4 h and 6-10 h after dosing Note: no predose sampling on C1D1 C1D15: predose and 2-12 h postdose C2D1: predose, 0.5-4 h and 6-10 h postdose Note: All predose samples should be collected within 2 hours of lenvatinib dosing. Note: Postdose samples not needed if lenvatinib administration is skipped. Cohorts A-F only Note: does not apply to Arm 2.
Blood for serum biomarker		X		X	X		X	X				Collect predose. Collect C1D1, C1D15, C2D1, C3D1, C5D1 and at EOT.
Blood for RNA Analysis		X			X		X	X				Collect predose on C1D1, C2D1, C3D1, C5D1, and at EOT.

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Blood for circulating tumor nucleic acids		X			X		X	X				Collect predose. C1D1, C2D1, C3D1, C5D1, and then D1 every 3 cycles, and at EOT.
Blood for plasma biomarkers		X			X		X	X				Collect predose. C1D1, C2D1, C3D1, C5D1 and then D1 every 3 cycles, and at EOT.
Blood for genetic analysis		X										Collect predose
Tumor blocks or slides	X											Collected during screening

Study Period	Screening	Intervention Period 21-Day Cycles						EOT	Post Intervention Visits			Notes
Cycle Number/Day		Cycle 1			Cycle 2		Cycle 3 Onward		Safety FU[a]	Efficacy FU	Survival FU	
		1	8	15	1	15	1					
Scheduling Window (Days)	-28 to -1		**±3**	**±3**	**±3**	**±3**	**±3**	At DC	30 Days After Last Dose (+ 7 d)	q9w[b] (± 7 d)	q12w (± 7 d)	
Patient-Reported Outcomes												
• EORTC QLQ-C30 • EORTC QLQ-disease-specific: • Breast (QLQ-BR23) • Ovarian (QLQ-OV28) • Gastric (QLQ-STO22) • Colorectal (QLQ-CR29) • GBM (QLQ-BN20) • Biliary (QLQ-BIL21) • Pancreatic (QLQ-PAN26) • EuroQol (EQ)-5D-5L		X			X		X	X	X			PRO assessments will be collected at baseline, every cycle through Cycle 13, Cycle 17, Cycle 21, EOT, and at the 30-day Safety FU visit. ePROs will also be obtained at the treatment discontinuation visit and the 30-day Safety Follow-up Visit. If the treatment discontinuation visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, ePROs do not need to be repeated. See additional details in Section 8.2.2.

AE = adverse event; aPTT = activated partial thromboplastin time; BICR = blinded independent central review; BP = blood pressure; BRCA = breast cancer susceptibility gene; BTC = biliary tract cancer; C1 = Cycle 1; C2 = Cycle 2; CR = complete response; CT = computed tomography; CV = cardiovascular; D1 = Day 1; D8 = Day 8; D15 = Day 15; DC = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC = European Organisation for the Research and Treatment of Cancer; EOT = end of treatment; ePRO = electronic patient-reported outcome; EQ-5D-5L = European Quality of Life 5-dimension 5-level; ER = estrogen receptor; FT4 = free thyroxine; FU = follow-up; GBM = glioblastoma; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; HER-2 = human epidermal growth factor receptor; HIV = human immunodeficiency virus; HR = heart rate; iCRO = imaging contract research organization; IDH 1/2 = isocitrate dehydrogenase 1/2; INR = International normalized ratio; IRT = interactive response technology; LDH = lactic dehydrogenase; LVEF = left ventricular ejection fraction; MGMT = O^6-methylguanine-DNA methyltransferase; MMR = mismatch repair; MRI = magnetic resonance imaging; MSI = microsatellite instability; MUGA = multigated acquisition; NYHA = New York Heart Association; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PE = physical examination; PK = pharmacokinetics; PRO = patient-reported outcome; PT = prothrombin time; q3w = once every 3 weeks; q6w = once every 6 weeks; q9w = once every 9 weeks; q12w = once every 12 weeks; q24w = once every 24 weeks; qd = once daily; QLQ = quality of life questionnaire; qw = once per week; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RNA = ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SIM = site imaging manual; T3 = triiodothyronine; TMB = tumor mutational burden; TNBC = triple-negative breast cancer; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Note: See Section 10.7 (Appendix 7) for country-specific requirements.

[a] If EOT Visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOT Visit and the Safety Follow-up Visit should be performed at the EOT Visit. End of treatment will be defined as the date when the participant discontinues all study treatments.

[b] During the Efficacy Follow-up Phase, tumor assessments should be performed according to the same imaging schedule used while receiving study intervention. Calculated from the date of first dose, imaging non-GBM cohorts should be performed q9w (63 days ±7 days) until Week 54 of study intervention (or sooner if clinically indicated) and q12w (84 days ±7 days) until Week 102. After Week 102, imaging should be performed q24w (168 days ±7 days) or sooner if clinically indicated. Imaging timing should follow calendar days. For the GBM cohort, imaging to be performed at 6 weeks (42 days to 49 days) from the date of treatment initiation. Subsequent tumor imaging should be performed q6w (42 days ±7 days) until Week 18 and then q9w thereafter or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed q12w (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed q24w, or sooner if clinically indicated.

[c] For non-GBM cohorts, tumor assessments will be based on chest, abdomen and pelvis CT or MRI. Historical scans performed within the screening period but before providing documented informed consent may be used if consistent with protocol requirements per SIM. All imaging visits have a scheduling window of ±7 days. Confirmation of baseline measurable disease per RECIST 1.1 by BICR is required before participant allocation/randomization. Imaging will be performed at 9 weeks (63 days ±7 days) from the date of treatment initiation. Subsequent tumor imaging should be performed q9w (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed q12w (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed q24w or sooner if clinically indicated (details to be provided in the SIM). For participants discontinuing for reasons other than PD, imaging should be performed q9w (until Week 54) and q12w thereafter. After Week 102 of FU, imaging should be performed q24w. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks before the EOT Visit. Imaging of any anatomy that shows disease either at screening or in subsequent evaluations will be required and should be submitted to the iCRO.

[d] For the GBM cohort, tumor assessments will be based on MRI of the brain. Historical scans performed within the screening period but before providing documented informed consent may be used if consistent with protocol requirements per SIM. Confirmation of baseline measurable disease per RANO by BICR is required before participant allocation. Imaging will be performed at 6 weeks (42 days to 49 days) from the date of treatment initiation. Subsequent tumor imaging should be performed q6w (42 days ±7 days) until Week 18 and then q9w thereafter or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed q12w (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed q24w or sooner if clinically indicated (details to be provided in the SIM). For participants discontinuing for reasons other than PD, imaging should be performed q6w until Week 18, q9w until Week 54 and q12w thereafter. After Week 102 of FU, imaging should be performed q24w. Imaging of any anatomy that shows disease either at screening or in subsequent evaluations will be required and should be submitted to the iCRO. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks before the EOT Visit. Imaging of any anatomy that shows disease either at screening or in subsequent evaluations will be required and should be submitted to the iCRO.

[e] Clinical laboratory assessments may be conducted any time within 72 hours before the scheduled visit, unless otherwise specified. Procedures/assessments should be performed before administration of study treatment.

2 INTRODUCTION

The purpose of this study is to determine the safety and efficacy in combining the programmed cell death 1 (PD-1) inhibitor pembrolizumab with the receptor tyrosine kinase inhibitor (RTKi) lenvatinib (also known as E7080 or MK-7902; hereafter referred to as lenvatinib) in participants with TNBC, ovarian cancer, gastric cancer, CRC, glioblastoma (GBM), BTC, or pancreatic cancer.

2.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across several indications.

Lenvatinib (also known as E7080 or MK-7902) inhibits the kinase activities of vascular endothelial growth factor (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 fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib also showed antiproliferative activity in cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α phosphorylation.

Once daily (qd) dosing of lenvatinib combined with pembrolizumab is currently being developed for the treatment of relapsed/refractory TNBC, ovarian cancer, gastric cancer, CRC, GBM or BTC.

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

2.1.1 Pharmaceutical and Therapeutic Background

2.1.1.1 Lenvatinib

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGRs 1 to 3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. and Hicklin, D. J. 2008] [Tammela, T. and Alitalo, K. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR also play important roles for tumor angiogenesis [Cross, M. J. and Claesson-Welsh L. 2001] [Lieu, C., et al 2011] [Limaverde-Sousa, G., et al 2014].

Lenvatinib is a potent multiple RTK inhibitor 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 very important for tumor angiogenesis.

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

2.1.1.2 Pembrolizumab

Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008]. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3 ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (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 solid tumors.

2.1.1.3 Scientific Rationale for the Combination of Lenvatinib with Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of cluster of differentiation 8 positive (CD8+) T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian cancer, CRC, pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and RCC.

In preclinical models, lenvatinib decreased the tumor-associated macrophage (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 with control. In the RAG murine tumor isograft tumor model, survival in the group treated with the combination was significantly longer than that of the respective monotherapy groups. In the CT26 murine tumor isograft model, treatment with the combination significantly increased the population of activated cytotoxic T-cells compared with that of the respective monotherapy groups [Kato, Y., et al 2019]. All treatments were well tolerated and severe body weight loss was not observed.

Based on these results, an open-label, Phase 1b/2 study (Study E7080-A001-111 [Study 111]) to assess the safety and preliminary antitumor activity of the combination of lenvatinib + pembrolizumab in participants with selected solid tumors is currently ongoing. Phase 1b of this study determined the MTD and RP2D as 20 mg lenvatinib qd in combination with 200 mg of pembrolizumab given intravenously (IV) every 3 weeks (q3w). The safety and efficacy of the combination at the lenvatinib RP2D is being assessed in the Phase 2 portion of the study that includes 6 cohorts (ie, NSCLC, RCC, EC, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck).

No dose reduction is allowed for pembrolizumab in this study.

2.1.2 Preclinical and Clinical Studies

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

2.1.3 Ongoing Clinical Studies

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

2.2 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.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In participants with TNBC (Cohort A), ovarian cancer (Cohort B), gastric cancer (Cohort C), CRC (Cohort D), glioblastoma (GBM, Cohort E), BTC (Cohort F), or pancreatic cancer (Cohort G), the objectives and endpoints outlined below will be evaluated.

Efficacy analyses will be performed by cohort/tumor type and RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ (Section 4.2.3.1), will be used for all tumor cohorts except GBM, which will use RANO Criteria (Section 4.2.3.1.3).

For Cohorts A-F, RECIST 1.1 (RANO for GBM) by investigator assessments will be used in the initial 30 enrolled participants. RECIST 1.1 (RANO for GBM) by BICR will be used in cohorts that expand to combine the initial 30 enrolled participants with the additional 70 to 100 expansion participants. For Cohort G, which will enroll 100 participants, RECIST 1.1 by BICR will be used.

For participants receiving pembrolizumab (Arm 1 only), modified RECIST 1.1 for immune-based therapeutics (iRECIST) will be used by investigators to assess tumor response and progression, and make treatment decisions, as well as for exploratory efficacy analyses (Section 4.2.3.1.2).

Objectives	Endpoints
Primary	
• Objective: To evaluate objective response rate (ORR) of pembrolizumab in combination with lenvatinib per tumor cohort based on RECIST 1.1 by investigator assessments in initial cohorts and BICR in cohorts that expand combining the initial and expansion cohorts (Cohorts A-F). In Cohort G, RECIST 1.1 by BICR will be used in all participants. (For participants with GBM, response will be assessed based on RANO criteria; all further references to RECIST 1.1 assessment apply to all cohorts except GBM.)	• Objective response (OR), complete response (CR), or partial response (PR)
• Objective: To assess safety and tolerability of treatment with pembrolizumab in combination with lenvatinib per tumor cohort assessed by the proportion of AEs.	• AEs • Discontinuation due to AEs
• Objective: To assess safety and tolerability of treatment with lenvatinib monotherapy assessed by the proportion of AEs.	• AEs • Discontinuation due to AEs

Objectives	Endpoints
Secondary	
• Objective: To evaluate disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) of pembrolizumab in combination with lenvatinib per tumor cohort based on RECIST 1.1 (RANO for GBM) by investigator assessments in initial cohorts and BICR in cohorts that expand combining the initial and expansion cohorts (Cohorts A-F). In Cohort G, RECIST 1.1 by BICR will be used in all participants.	• Disease control, defined as best overall response of CR, PR, or stable disease • DOR, determined by disease assessment defined as the time from the earliest date of qualifying response until the earliest date of disease progression or death from any cause, whichever comes first. • PFS, defined as the time from the first day of study intervention to the day of the first documentation of disease progression or death from any cause, whichever occurs first.
• Objective: To evaluate overall survival (OS) of pembrolizumab in combination with lenvatinib per tumor cohort.	• OS, defined as the time from the first day of study intervention to the day of death from any cause.
• Objective: To evaluate ORR, DCR, DOR, PFS, and OS of lenvatinib monotherapy (Cohort D) based on RECIST 1.1 by BICR.	• OR • DCR • DOR • PFS • OS
• Objective: To characterize the population pharmacokinetics (PK) of lenvatinib when coadministered with pembrolizumab in participants per tumor cohort (Cohorts A-F only).	• Plasma concentration of lenvatinib.

Objectives	Endpoints
Tertiary/Exploratory	
• Objective: To evaluate ORR, DCR, DOR, and PFS of pembrolizumab in combination with lenvatinib per tumor cohort based on iRECIST (non-GBM cohorts) by investigator assessments.	• OR • DCR • DOR • PFS
• Objective: To evaluate ORR, DCR, DOR, PFS, and OS of pembrolizumab in combination with lenvatinib relative to lenvatinib monotherapy per tumor cohort.	• OR • DCR • DOR • PFS • OS
• Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers per tumor cohort that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab and lenvatinib in all participants.	• Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

Objectives	Endpoints
• Objective: To evaluate changes in patient-reported outcomes per tumor cohort from baseline using below PROs and to evaluate time to deterioration (TTD) in the EORTC-QLQ-C30 subscales: - EORTC-QLQ-C30 - EORTC QLQ-disease-specific: ◦ Breast (QLQ-BR23) ◦ Ovarian (QLQ-OV28) ◦ Gastric (QLQ-STO22) ◦ Colorectal (QLQ-CR29) ◦ GBM (QLQ-BN20) ◦ Biliary (QLQ-BIL21) ◦ Pancreatic (QLQ-PAN26) - EuroQol (EQ)-5D-5L	• HRQoL will be assessed using the global score of the EORTC • Health utilities, assessed using the EQ-5D-5L • TTD evaluated for EORTC QLQ-C30 subscales

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, open-label, Phase 2 study to evaluate the efficacy and safety of lenvatinib 20 mg qd in combination with pembrolizumab (Arm 1) in previously treated participants with TNBC (Cohort A), ovarian cancer (Cohort B), gastric cancer (Cohort C), CRC (Cohort D), GBM (Cohort E), BTC (Cohort F), or pancreatic cancer (Cohort G). The efficacy and safety of lenvatinib monotherapy (24 mg qd, Arm 2) will be evaluated in participants with CRC (Cohort D).

Initially, approximately 180 eligible participants will be stratified by tumor cohort (Cohorts A-F; 30 participants per cohort) and enrolled to receive lenvatinib 20 mg orally qd plus pembrolizumab 200 mg (IV q3w) for up to 35 administrations or until disease progression per RECIST 1.1 or RANO for the GBM cohort, unacceptable toxicity, withdrawal of consent, initiation of new anticancer treatment, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, pregnancy, administrative reasons requiring cessation of treatment, or death. Pembrolizumab treatment will be discontinued once the participant has received 35 administrations (approximately 2 years). Participants in Arm 1 and Arm 2 may continue

treatment with lenvatinib beyond 2 years if they experience clinical benefit according to the PI, with Sponsor consultation. Participants may discontinue treatment with pembrolizumab and lenvatinib if a CR has been attained per RECIST 1.1 (RANO for the GBM cohort) and they have been treated for at least 24 weeks, receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.

Potential for cohort expansion will be assessed for Cohorts A-F as described in Section 4.1.1. Additionally, 100 eligible participants with pancreatic cancer (Cohort G) will be enrolled to receive lenvatinib 20 mg orally qd plus pembrolizumab 200 mg (IV q3w) as described above. Enrollment into Cohort G will proceed as described in Section 4.1.2.

Participants will be permitted to continue treatment beyond RECIST 1.1- or RANO-defined progression (Arm 1 only) as long as investigator-assessed clinical stability is observed, the participant is tolerating study intervention (Section 8.2.1.5 or Section 8.2.1.6) and after obtaining documented informed consent addendum. Treatment beyond confirmed PD per iRECIST or RANO may be permitted on Sponsor consultation.

The primary objective of this study is to evaluate the ORR of pembrolizumab + lenvatinib for each indication/cohort separately. Additionally, the ORR of lenvatinib monotherapy will be evaluated to address a secondary objective, and the ORR of pembrolizumab + lenvatinib combination therapy relative to lenvatinib monotherapy will be evaluated to address a tertiary objective in participants with CRC (Cohort D). For all cohorts (except GBM), on-study imaging assessments will be performed every 9 weeks (q9w; 63 days ±7 days) from the date of treatment initiation until 54 weeks (378 days ±7 days). After 54 weeks, imaging will be performed every 12 weeks (84 days ±7 days) or sooner, if clinically indicated, until Week 102. After Week 102, imaging should be performed q24w, or sooner if clinically indicated. For participants with GBM, imaging will be performed at 6 weeks (42 days to 49 days) from the date of treatment initiation. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) until Week 18 and then every 9 weeks thereafter or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed q24w, or sooner if clinically indicated. Imaging should follow calendar days and be independent of treatment delays. RECIST 1.1 (or RANO for participants with GBM) will be used by the site for treatment decisions until the first radiologic evidence of PD. Participants who experience confirmed disease progression or start a new anticancer therapy will move into survival follow-up and should be contacted by telephone or visit approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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.

4.1.1 Cohort Expansion (Cohorts A-F)

Potential for cohort expansion will be assessed for each cohort using IAs for efficacy, based on investigator assessment. The IAs will occur after the initial 30 enrolled participants have been followed up for approximately 6 months after study entry. For cohorts with slow enrollment, IAs may take place when the majority of participants have been followed up for 6 months from study entry. The results of each IA will be reviewed by the Sponsor, and recommendations for cohort expansion will be provided. Further details are provided in Section 9 – Statistical Analysis Plan (SAP).

If cohort expansion is recommended, the first 30 participants enrolled before the expansion may continue to receive treatment for up to 35 administrations of pembrolizumab from study entry or until disease progression per RECIST 1.1 (or RANO for the GBM cohort), unacceptable toxicity, withdrawal of consent, initiation of new anticancer treatment, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, administrative reasons requiring cessation of treatment or death.

If cohort expansion is not recommended, participants experiencing response will be allowed to continue receiving treatment for up to 35 administrations of pembrolizumab from study entry or until disease progression per RECIST 1.1 (or RANO for the glioblastoma GBM cohort), unacceptable toxicity, withdrawal of consent, initiation of new anticancer treatment, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant administrative reasons requiring cessation of treatment or death.

Cohorts C, E, and F will each be expanded to include a total of approximately 100 participants, 30 from the initial cohort and an additional 70 participants in the expansion phase, each allocated to receive pembrolizumab + lenvatinib combination therapy to assess efficacy and safety in these disease states. Cohorts A (TNBC) and B (ovarian cancer) will not be included in the expansion phase due to changes which have occurred in the treatment landscape for these malignancies since the study was initiated.

Cohort D (CRC) will be expanded to include a total of 130 participants: 30 from the initial cohort and an additional 100 participants in the expansion phase. The last approximately 60 participants will be randomized 1:1 to receive pembrolizumab + lenvatinib (Arm 1) or lenvatinib monotherapy (Arm 2). The goal of this randomization is to assess the contribution of lenvatinib in the overall treatment effect of the pembrolizumab + lenvatinib combination. If a clinically meaningful response is not observed, the Sponsor may elect not to include a randomization arm and may stop enrollment.

4.1.2 Cohort G (Pancreatic Cancer)

Based on the efficacy results and manageable safety profile of pembrolizumab + lenvatinib noted in Study E7080-A001-111 (KEYNOTE-146; NCT02501096) and the LEAP program to date, as well as the high unmet need in pancreatic cancer (Section 4.2.2), 100 participants with pancreatic cancer will be enrolled into Cohort G. An IA will be performed when

approximately 30 participants in Cohort G have been followed up for approximately 6 months. Enrollment will continue before and during the IA. If there is evidence of efficacy based on the IA, enrollment into Cohort G will continue to approximately 100 participants; otherwise, enrollment could be stopped (Section 9.7).

4.1.3 Early Termination of Cohort(s) and/or Discontinuation of Cohort Enrollment

Specific cohort(s) within the study may be terminated early and/or further enrollment stopped for 1 or both of the following reasons:

- Extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population in the specific cohort(s) is unacceptable.
- Emerging information from other studies is such that the participant safety or the risk/benefit ratio to a cohort population is unacceptable.

Continuation of study intervention may be allowed for a study participant who benefits from ongoing study intervention, if justified by the investigator and documented in a Sponsor consultation form.

4.2 Scientific Rationale for Study Design

This multicenter, open-label, Phase 2 study was designed as a proof-of-concept in single treatment group disease cohorts whose lines of therapy have no defined standard of care to assess the efficacy and safety of lenvatinib in combination with pembrolizumab in participants with advanced: TNBC, ovarian cancer, gastric cancer, CRC, BTC, glioblastoma, and pancreatic cancer.

4.2.1 Cohorts A-F

The starting sample size of 30 participants per cohort (Cohorts A-F) is estimated based on the primary endpoint and the required target ORR to produce a confidence interval for the true ORR. A cohort which achieves its target ORR will be expanded to a total of 100 participants (Cohorts C, E, and F) or 130 participants (Cohort D). See Section 9.9 for additional information regarding sample size.

The last approximately 60 participants in Cohort D (CRC) will be randomized 1:1 to receive either pembrolizumab + lenvatinib (Arm 1) or lenvatinib monotherapy (Arm 2), as described in Section 4.1.1, to assess the contribution of lenvatinib in the overall treatment effect of the pembrolizumab + lenvatinib combination in these tumor types.

4.2.2 Cohort G (Pancreatic Cancer)

Pancreatic cancer is the fourth leading cause of cancer-related death in the US [Siegel, R. L., et al 2020] with adenocarcinoma representing approximately 90% of all pancreatic cancers. Surgical excision represents the only option for cure, however 80% of patients are diagnosed at an inoperable stage. There is a high unmet medical need for metastatic pancreatic cancer with a survival at 5 years of only 3%. Based on the efficacy observed across diseases to date

in the lenvatinib-pembrolizumab program and the poor outcomes in pancreatic cancer, the Sponsor is pursuing the impact of this combination in pancreatic cancer.

One hundred participants will be enrolled into Cohort G (pancreatic cancer). See Section 9.9 for additional information regarding sample size.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

This study will use OR as the primary endpoint based on RECIST 1.1 criteria (or RANO for GBM) as assessed by investigator in initial cohorts and by BICR for cohorts that expand (Cohorts C-F) as well as for Cohort G. OR is an acceptable measure of clinical benefit for a late stage study that shows superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 (or RANO for GBM) to assess OR is typically considered acceptable by regulatory authorities. Images will be read by BICR blinded to treatment assignment to minimize bias in the response assessments.

DCR, DOR, and PFS as assessed by BICR according to RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ and OS will serve as additional measures of efficacy and are commonly accepted endpoints by both regulatory authorities and the oncology community.

iRECIST may also be used by the local site to make treatment decisions once PD has been documented per RECIST 1.1 in non-GBM cohorts.

Measurable disease will be confirmed centrally at enrollment, before participant allocation, to ensure that the assessment of measurable disease is accurate. These endpoints have been chosen as ancillary markers of efficacy in a population with few treatment options.

4.2.3.1.1 RECIST 1.1

RECIST 1.1 (RANO for GBM) will be used by investigator assessment when determining eligibility and confirmed prospectively by BICR before allocation.

RECIST 1.1 (RANO for GBM) will be used by the BICR when assessing images for efficacy measures in cohorts that expand (Cohorts C-F), which will combine the initial cohort and the expansion cohort, as well as Cohort G. Although traditional RECIST 1.1 references 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.

Refer to Section 8.2.1.4 for details on RECIST 1.1 (for non-GBM cohorts) and Section 8.2.1.6 on RANO (for GBM).

4.2.3.1.2 Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen after treatment with immunotherapeutic agents (Section 8.2.1.5). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and participants treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not fully capture the treatment benefits from immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001, 7% of evaluable participants experienced delayed or early tumor pseudoprogression. Of note, participants who had PD by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer OS than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants [Hodi, F. S., et al 2016]. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

iRECIST assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression, and to make treatment decisions, as well as for exploratory efficacy analyses where specified.

For Cohorts A-G (combination therapy only), the ORR, DOR, DCR and PFS will also be evaluated per iRECIST by investigator assessment.

Refer to Section 8.2.1.5 for details on iRECIST.

4.2.3.1.3 Response Assessment in Neuro-Oncology (RANO)

RANO criteria have been the preferred criteria for assessing responses in GBM studies since their publication in 2010 [Wen, P. Y., et al 2010] and incorporate measurements of tumor size as shown by contrast-enhanced magnetic resonance imaging (MRI) with qualitative assessment of both enhancing and nonenhancing disease, and information on steroid dosing and participant functional performance status. Response assessments will be performed by investigators and by BICR.

RANO also makes provisions for the pseudoprogression frequently seen after radiotherapy. The AVAglio study [Gilbert, M. R., et al 2014] (BO21990, NCT00943826) modified the Macdonald criteria by using T2/fluid-attenuated inversion recovery (FLAIR) imaging,

clinical assessment, and the qualitative review of all nonindex lesions to correct for non-contrast-enhancing lesions, residual disease, difficult to measure lesions, and pseudoprogression. The RANO Working Group further refined the measurements by relaxing criteria around clinical progression and in the timing, criteria, and confirmation of scans to detect pseudoprogression [Chinot, O. L., et al 2013].

The Radiation Therapy Oncology Group (RTOG) and American College of Radiology Imaging Network (ACRIN) (RTOG0625/ACRIN6677) evaluated the predictive ability of RANO in 107 patients with recurrent GBM treated with bevacizumab, irinotecan, or temozolomide [Boxerman, J. L., et al 2013]. The study concluded that progression observed at 8 and 16 weeks of bevacizumab treatment on 2D-T1 and 3D-T1 imaging, had highly significant prognostic value for OS. However, progression detected by FLAIR alone did not correlate with OS and added minimal additional benefit to other imaging technologies.

4.2.3.2 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) and serious AEs (SAEs) and changes in vital signs and laboratory values. AEs will be assessed as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version [4.0].

4.2.3.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities. As part of the analyses for this study, participants will provide information regarding their health-related quality of life (HRQoL) via the following assessment tools: European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and European Quality of Life 5-dimension 5-level (EQ-5D-5L) questionnaires. In addition, the following cohort-specific assessments tools will be used: QLQ-BR23 (Breast), QLQ-OV28 (Ovarian), QLQ-STO22 (Gastric), QLQ-CR29 (Colorectal), QLQ-BN20 (GBM), QLQ-BIL21 (Biliary), and QLQ-PAN26 (Pancreatic).

The PROs will be administered in the order below:

- EORTC- QLQ-C30
- EORTC- QLQ- disease-specific
- EQ-5D-5L

These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.3.3.1 EORTC QLQ-C30

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 status/quality of life (QoL) scale (items 29 and 30) [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies [Aaronson, N. K., et al 1993].

4.2.3.3.2 EQ-5D-5L

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

4.2.3.3.3 Cohort-Specific Patient-reported Outcomes

The EORTC QLQ-BR23, QLQ-OV28, QLQ-STO22, QLQ-CR29, QLQ-BN20, QLQ-BIL21, and QLQ-PAN26 are disease-specific questionnaires developed and validated to address measurements specific to breast, ovarian cancer, gastric cancer, colorectal, GBM, BTC, and pancreatic cancers, respectively. They are a few of multiple disease-specific modules developed by the EORTC QLG (Quality of Life Group) designed for use in clinical studies, to be administered in addition to the QLQ-C30 to assess disease-specific treatment measurements.

4.2.3.3.3.1 EORTC QLQ-BR23

EORTC QLQ-BR23 is a QoL questionnaire developed to assess the extent of symptoms or problems in participants receiving treatment for breast cancer. The tool is used in conjunction with the EORTC QLQ-C30 and follows the same 4-point scale described above. The tool consists of 23 questions containing 4 functioning scales (body image, sexual functioning, sexual enjoyment, future perspective) and 4 symptom scales (arm symptoms, breast symptoms, systemic therapy side effects, upset by hair loss). The recall period is one week for all questions except those on sexual functioning which have a recall period of 4 weeks.

4.2.3.3.3.2 EORTC QLQ-OV28

The EORTC QLQ-OV28 is a cancer module meant for use among ovarian cancer patients varying in disease state and treatment modality (ie, surgical procedure, chemotherapy, radiotherapy, etc.). The module comprises 28 questions assessing functional scales including body image, sexuality, and attitude to disease/treatment as well as symptoms (including abdominal/GI issues, peripheral neuropathy, hormonal/menopausal symptoms, other chemotherapy side effects, and hair loss).

4.2.3.3.3.3 EORTC QLQ-STO22

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

4.2.3.3.3.4 EORTC QLQ-CR29

The EORTC QLQ-CR29, a supplemental CRC-specific module, comprises multi-item and single-item measures of CRC-associated symptoms and impact. The measure includes 4 scales assessing urinary frequency, stool frequency, blood and mucus in stool, and body image, and 19 single items assessing common problems after treatment of CRC.

4.2.3.3.3.5 EORTC QLQ-BN20

The EORTC QLQ-BN20 is a disease-specific questionnaire developed and validated to address measurements specific to brain cancer [Taphoorn, M. J. B., et al 2010]. It is one of multiple disease-specific modules developed by the EORTC QLG designed for use in clinical studies, to be administered in addition to the QLQ-C30 to assess disease-specific treatment measurements. It consists of 20 items containing 4 scales (“future uncertainties”, “visual disorder”, “motor dysfunction”, and “communication deficit”) and 7 single items.

4.2.3.3.3.6 EORTC QLQ-BIL21

The EORTC QLQ-BIL21 is a disease-specific questionnaire intended for use among patients with cholangiocarcinoma and gallbladder cancer, who vary in disease stage and treatments. The module comprises 21 questions assessing disease symptoms (including jaundice, eating, tiredness, pain and anxiety) and side effects of treatment.

4.2.3.3.3.7 EORTC QLQ-PAN26

The EORTC QLQ-PAN26 is a disease-specific questionnaire developed and validated to address HRQoL issues specific to pancreatic cancer and is intended to supplement the EORTC QLQ-C30. The module includes 26 questions evaluating symptoms related to disease and treatment (eg, pain, indigestion, altered bowel habit, and side effects), as well as

emotional difficulties related to pancreatic cancer (eg, body image, sexuality, and health care satisfaction). There are 7 multi-item scale scores consisting of 2 to 4 items and 10 single-item scores.

4.2.3.4 Pharmacokinetic Endpoints

Based on PK data obtained in this study and from other studies, a population PK analysis may be performed to characterize PK parameters of lenvatinib when coadministered with pembrolizumab to support the proposed dosing regimen. In addition, exposure-response (E-R) analyses for safety and efficacy endpoints for the indications studied in this protocol may be performed.

4.2.3.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.3.6 Planned Exploratory Biomarker Research

CCI

CCI

[redacted]

CCI

[redacted]

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

4.3.1.1 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 EC, and 1 had melanoma. There were 2 dose-limiting toxicities (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 [Taylor, M. H., et al 2016].

Based on the preclinical results, Study 111/KEYNOTE-146 was initiated. Study E7080-A001-111/KEYNOTE-146 is an ongoing multicohort Phase 1b/2 clinical study to assess the safety and preliminary antitumor activity of lenvatinib in combination with pembrolizumab in 6 types of biomarker-unselected metastatic solid tumors, including NSCLC, that have progressed after treatment with approved therapies or for which there are no standard effective therapies available.

Phase 1b of this study determined the MTD and recommended Phase 2 dose (RP2D) as 20 mg lenvatinib qd in combination with pembrolizumab 200 mg IV q3w. The primary endpoint of the initial part of Phase 2 is ORR after 24 weeks of treatment, with select secondary endpoints, including OR, DCR, PFS, and DOR. The safety and efficacy of the combination at the lenvatinib RP2D is being assessed in the Phase 2 portion of the study that includes 6 cohorts (NSCLC, RCC, endometrial carcinoma, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck).

Based on the promising antitumor efficacy and tolerable safety profile seen in both the EC and RCC expansion cohorts from Study 111/KEYNOTE-146 [Makker, V., et al 2018], two Phase 3 studies have been initiated for both of these tumor types, Study E7080-G000-309/KEYNOTE-775 and Study E7080-G000-307/KEYNOTE-581.

Based on modeling of lenvatinib PK data, the safest dose of lenvatinib monotherapy that provides the highest efficacy is 25 mg qd. The dose selected for the lenvatinib monotherapy

arm, 24 mg qd, was selected to simplify the dose reduction scheme, and is the recommended dose in locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (refer to the lenvatinib IB).

4.3.1.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg q3w. Based on the totality of data generated in the KEYTRUDA development program, 200 mg q3w is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies showing flat dose- and exposure- efficacy relationships from 2 mg/kg q3w to 10 mg/kg q2w,
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg q3w across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based PK [PBPK] analysis) at 200 mg q3w.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg q3w versus 10 mg/kg q3w (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg q3w versus 10 mg/kg q2w (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies showed flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure.

The 2 mg/kg (or 200 mg fixed dose) q3w provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg q3w as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg q3w. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively showed saturation of PD-1 in systemic circulation at doses much lower than 200 mg q3w. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg q3w achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap

in the distribution of exposures from the 200 mg q3w fixed dose and 2 mg/kg q3w dose. Supported by these PK characteristics, and given that fixed dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg q3w fixed dose was selected for evaluation across all pembrolizumab protocols.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg q3w up to 35 administrations. The maximum dose/exposure of lenvatinib allowed in this study is 20 mg qd for participants receiving pembrolizumab + lenvatinib combination therapy (Cohorts A-G) and 24 mg qd for participants receiving lenvatinib monotherapy (Cohort D only). Participants in Arm 1 may continue treatment with lenvatinib after discontinuation or completion of 35 treatments (approximately 2 years) of pembrolizumab if they experience clinical benefit according to the PI with Sponsor consultation until disease progression or unacceptable toxicity. Participants in Arm 2 may continue treatment with lenvatinib beyond 2 years if they experience clinical benefit according to the PI with Sponsor consultation until disease progression or unacceptable toxicity.

4.4 Beginning and End of Study Definition

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

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

5 STUDY POPULATION

Participants with TNBC, ovarian cancer, gastric cancer, CRC, GBM, BTC, or pancreatic cancer.

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

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Have a histologically or cytologically documented, advanced (metastatic and/or unresectable) solid tumor that is incurable and for which prior standard systemic therapy has failed in one of the following cohorts:

Cohort A	Triple-Negative Breast Cancer
Cohort B	Ovarian Cancer
Cohort C	Gastric Cancer
Cohort D	Colorectal Cancer
Cohort E	Glioblastoma
Cohort F	BTC (intrahepatic, extrahepatic cholangiocarcinoma and gall bladder cancer; excludes Ampulla of Vater)
Cohort G	Pancreatic Cancer (ductal adenocarcinoma)

2. Participants must have fulfilled cohort-specific requirements regarding prior (line of therapy) treatments. Refer to Sections 5.1.1 through 5.1.7 for cohort-specific inclusion criteria).

   Note: Merck will be using American Joint Committee on Cancer (AJCC) Staging manual (Eighth Edition) to review tumor node metastasis staging classification to ensure consistency of participant enrollment.

3. Participants must have progressed on or since the last treatment.

4. Have measurable disease per RECIST 1.1 (RANO for the GBM cohort) as assessed by the local site investigator/radiology and confirmed by BICR. Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.

5. Have provided a PD-L1 evaluable archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Fine-needle aspiration biopsies are not acceptable.

   Note: If participants have only 1 measurable lesion per RECIST 1.1, the biopsy specimen should be obtained from a nontarget lesion or archival tissue.

Demographics

6. Participants are at least 18 years of age; male or female for gastric cancer, GBM, TNBC, CRC, BTC, and pancreatic cancer cohorts; female only for ovarian cancer.

7. Life expectancy of 12 weeks or more.

Male Participants

8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of lenvatinib:

   - 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.

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

Female Participants

9. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

   - Is not a woman of childbearing potential (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 120 days post pembrolizumab or 30 days post lenvatinib, whichever occurs last. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   - 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 located in Appendix 2.

   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.

Informed Consent

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

Additional Categories

11. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 assessed within 3 days before allocation/randomization.

12. Have adequate organ function as defined in the following table (Table 1). Samples must be collected within 7 days before the start of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥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 and biliary tract cancer)
Albumin	≥3 g/dL
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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

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

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

13. Have adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no change in antihypertensive medications within 1 week before randomization.

    See Section 10.7 (Appendix 7) for country-specific requirements.

5.1.1 Triple-Negative Breast Cancer-Specific Inclusion Criteria

To be eligible for inclusion in this study, the breast cancer participant must:

14. Have received one or 2 prior lines of therapy. Study medication will treat TNBC (2L/3L).

    Note: Participants must have been treated with a taxane and anthracycline at some time during their course of treatment to meet eligibility.

    Note: Prior surgical intervention +/- adjuvant chemotherapy is not considered a line of therapy unless such treatments were completed within 6 months before the current tumor recurrence.

    Note: Prior therapy of metastatic or unresectable disease is considered a line of therapy.

    Note: Definitive surgical procedures with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

    Note: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Switching (eg, cisplatin to carboplatin) for toxicity will **NOT** be considered a line of therapy change (unless a delay in treatment is required for ≥2 months). Switching for toxicity will be considered a line of therapy change if there is a change in mechanism of action between the therapies. Interruptions (eg, oxaliplatin in FOLFOX) will NOT be considered a line of therapy change (unless the interruption is ≥2 months).

    Note: Maintenance regimens administered with the purpose of maintaining response after treatment will not be considered lines of therapy.

15. Have Lactate Dehydrogenase (LDH) <2.0 × ULN.

16. Have locally determined results for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 tumor analyses.

5.1.2 Ovarian Cancer-Specific Inclusion Criteria

To be eligible for inclusion in this study, the ovarian cancer participant must:

17. Have primary ovarian cancer and have received 3 prior lines of therapy. Study medication will treat ovarian cancer (4L).

    Note: Neoadjuvant/adjuvant systemic cytotoxic chemotherapy used in the initial treatment is considered prior line of therapy.

    Note: All systemic cytotoxic chemotherapy, including antibody–drug conjugates with a cytotoxic warhead, are considered prior lines of therapy.

Note: Definitive surgical intervention with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

Note: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Switching (eg, cisplatin to carboplatin) for toxicity will **NOT** be considered a line of therapy change (unless a delay in treatment is required for ≥2 months). Switching for toxicity will be considered a line of therapy change if there is a change in mechanism of action between the therapies. Interruptions will NOT be considered a line of therapy change (unless the interruption is ≥2 months, eg, rechallenge with platinum in ovarian cancer).

Note: Maintenance regimens administered with the purpose of maintaining CR or PR will not be considered lines of therapy.

5.1.3 Gastric Cancer-Specific Inclusion Criteria

To be eligible for inclusion in this study, the gastric cancer participant must:

18. Have received 2 prior lines of therapy. Study medication will treat gastric cancer (3L).

Note: Gastric cancer will include participants with both gastric and gastroesophageal junction (GEJ) adenocarcinoma. Participants with squamous cell carcinoma histology are not eligible.

Note: Prior neoadjuvant or adjuvant systemic cytotoxic chemotherapy used in the initial treatment is not considered a prior line of therapy unless such treatments were completed within 12 months before the current tumor recurrence.

Note: All systemic cytotoxic chemotherapy, including antibody–drug conjugates with a cytotoxic warhead, are considered prior lines of therapy.

Note: Definitive surgical intervention with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

Note: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Switching (eg, cisplatin to carboplatin) for toxicity will **NOT** be considered a line of therapy change (unless a delay in treatment is required for ≥2 months). Switching for toxicity will be considered a line of therapy change if there is a change in mechanism of action between the therapies. Interruptions will NOT be considered a line of therapy change (unless the interruption is ≥2 months).

Note: Maintenance regimens administered with the purpose of maintaining response after treatment will not be considered lines of therapy.

5.1.4 Colorectal Cancer-Specific Inclusion Criteria

To be eligible for inclusion in this study, the CRC participant must:

19. Have received 2 prior lines of therapy. Study medication will treat CRC (3L).

    Note: Participants must have received oxaliplatin and irinotecan in separate lines of therapy, these are usually provided with fluoropyrimidine (eg, FOLFOX and FOLFIRI).

    Note: Capecitabine is acceptable as equivalent to fluoropyrimidine in prior therapy (XOLFOX, XOLFIRI)

    Note: Participants who have previously received fluoropyrimidine, oxaliplatin, and irinotecan as part of the same and only chemotherapy regimen, eg, FOLFOXIRI or FOLFIRINOX, will be considered 2L patients, and do not qualify for the study.

    Note: Only the participants with the mutations listed below may receive FOLFOXIRI or FOLFIRINOX as a line of therapy which covers the oxaliplatin and irinotecan requirement. The participant must have also received ALL the following agents necessary to treat the underlying mutation, if approved and locally available in the country where the participant is enrolled, to achieve the 2 prior lines of therapy required to be eligible for the study.

    a. At least one of the anti-EGFR monoclonal antibodies (cetuximab or panitumumab) for RAS (KRAS/NRAS) WT participants.

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

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

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

    Note: All systemic cytotoxic chemotherapy, including antibody–drug conjugates with a cytotoxic warhead, are considered prior lines of therapy.

    Note: Definitive surgical intervention with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

    Note: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Switching (eg, cisplatin to carboplatin) will **NOT** be considered a line of therapy change (unless a delay in treatment is required for ≥2 months). Switching for toxicity will be considered a line of therapy

change if there is a change in mechanism of action between the therapies. Interruptions will NOT be considered a line of therapy change (unless the interruption is ≥2 months).

Note: Maintenance regimens administered with the purpose of maintaining response after treatment will not be considered lines of therapy.

Note: Hyperthermic intraperitoneal chemotherapy (HIPEC) or other locoregional therapies are allowed but will not be counted as prior lines of therapies.

5.1.5 GBM Specific Inclusion Criteria

To be eligible for inclusion in this study, the GBM participant must:

20. Have failed initial systemic therapy for newly diagnosed GBM. Study medication will treat GBM (2L)

    Note: Previous first-line therapy with at least radiotherapy using standard dosing of central nervous system (CNS) radiation including 60 Gy in 30 fractions, 59.4 Gy in 1.8 Gy per fraction or equivalent.

    Note: Relapse is defined as progression after initial therapy (i.e., radiation ± chemotherapy).

    Note: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Switching (eg, cisplatin to carboplatin) for toxicity will **NOT** be considered a line of therapy change (unless a delay in treatment is required for ≥2 months). Switching for toxicity will be considered a line of therapy change if there is a change in mechanism of action between the therapies. Interruptions will NOT be considered a line of therapy change (unless the interruption is ≥2 months).

21. Have the following time periods elapsed before the projected start of scheduled study treatment:

- At least 3 weeks from prior surgical resection

  Participants having undergone recent resection of recurrent or progressive tumor will be eligible as long as they have recovered from the effects of surgical intervention and have measurable residual disease before starting study therapy.

- At least 1 week from stereotactic biopsy

- At least 6 months from completion of prior radiotherapy

  If participants have not passed an interval of at least 6 months, they may still be eligible if they meet the following criteria: New area of enhancement outside the 80% isodose line of the original radiation field as determined by the treating investigator.

- At least 4 weeks (or 5 half-lives, whichever is shorter) from any investigational agent
- At least 4 weeks from cytotoxic therapy
  - Exceptions:
    - At least 23 days for temozolomide
    - At least 6 weeks from nitrosoureas
  - At least 4 weeks (or 5 half-lives, whichever is shorter) for daily administered chemotherapeutics
- At least 6 weeks from antibodies
- At least 4 weeks (or 5 half-lives, whichever is shorter) from other antitumor therapies and 1 week for cancer vaccines

22. Be neurologically stable (eg, without a progression of neurologic symptoms or requiring escalating doses of systemic steroid therapy within last 2 weeks) and clinically stable.

23. Has histologically confirmed World Health Organization Grade 4 glioblastoma.

5.1.6 Biliary Tract Cancer-Specific Inclusion Criteria

To be eligible for inclusion in this study, the BTC participant must:

24. Have received 1 prior line of therapy. Study medication will treat BTC (2L)

    Note: Prior adjuvant systemic cytotoxic chemotherapy used in the initial treatment is not considered a prior line of therapy unless such treatments were completed within 6 months before the current tumor recurrence.

    Note: All systemic cytotoxic chemotherapy, including antibody–drug conjugates with a cytotoxic warhead, are considered prior lines of therapy.

    Note: Definitive surgical intervention with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

    Note: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Switching (eg, cisplatin to carboplatin) for toxicity will **NOT** be considered a line of therapy change (unless a delay in treatment is required for ≥2 months). Switching for toxicity will be considered a line of therapy change if there is a change in mechanism of action between the therapies. Interruptions (eg, oxaliplatin in FOLFOX) will NOT be considered a line of therapy change (unless the interruption is ≥2 months).

Note: Maintenance regimens administered with the purpose of maintaining response after treatment will not be considered lines of therapy.

Note: TACE or other locoregional therapies are allowed but will not be counted as prior lines of therapies.

25. Has Child-Pugh Score, Class A: well-compensated disease. Child-Pugh Score of 5 to 6.

5.1.7 Pancreatic Cancer-Specific Inclusion Criteria

To be eligible for inclusion in this study, the pancreatic cancer participant must:

26. Have pathologically (histologically or cytologically) confirmed pancreatic ductal adenocarcinoma that is metastatic at enrollment.

    Note: Histology other than adenocarcinoma, including mixed histologies, is not allowed.

27. Have received one or 2 prior lines of therapy. Study medication will treat pancreatic cancer (2L/3L); the 3L pancreatic cancer population will be capped at 40%.

28. Have received prior therapy with at least 1 (platinum-containing regimen or gemcitabine-containing regimen) but no more than 2 prior systemic therapies for unresectable or metastatic pancreatic cancer.

    Note: Participants with known deleterious or suspected germline breast cancer susceptibility gene mutation (gBRCAm) metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen should have received olaparib maintenance treatment to be eligible, if this agent is approved and locally available in the country where the participant is randomized.

    Note: Prior adjuvant and neoadjuvant systemic cytotoxic chemotherapy used in the initial treatment is not considered a prior line of therapy unless such treatments were completed within 6 months before the current tumor recurrence.

    Note: All systemic cytotoxic chemotherapy, including antibody–drug conjugates with a cytotoxic warhead, are considered prior lines of therapy.

    Note: Definitive surgical intervention with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are NOT considered prior lines of therapy.

    Note: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Switching (eg, cisplatin to carboplatin) for toxicity will NOT be considered a line of therapy change (unless a delay in treatment is required for ≥2 months). Switching for toxicity will be considered a line of therapy change if there is a change in mechanism of action between the therapies.

Interruptions (eg, oxaliplatin in FOLFOX) will NOT be considered a line of therapy change (unless the interruption is ≥2 months).

Note: Locoregional therapies will not be counted as a line of therapy.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has gastrointestinal malabsorption or any other condition that might affect the absorption of lenvatinib.

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

   Note: This exclusion applies to all cohorts except the ovarian cancer cohort.

3. Has radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation. The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.

   Note: Participants with portal vein invasion (Vp4), inferior vena cava, or cardiac involvement based on imaging in the BTC cohort are not eligible for enrollment.

4. Has clinically significant hemoptysis or tumor bleeding within 2 weeks before the first dose of study intervention.

5. Has significant cardiovascular impairment within 12 months of the first dose of study intervention, such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or cerebrovascular accident (CVA), or cardiac arrhythmia associated with hemodynamic instability.

   Note: Medically controlled arrhythmia would be permitted.

6. Has a history of arterial thromboembolism within 12 months of start of study intervention.

7. 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.

8. Has a serious nonhealing wound, ulcer or bone fracture.

9. Has had a major surgical procedure within 3 weeks before the first dose of study interventions.

   Note: Adequate wound healing after a major surgical procedure must be assessed clinically, independent of time elapsed for eligibility.

10. Has biologic response modifiers therapy (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.

11. Has pre-existing ≥Grade 3 gastrointestinal (GI) or nongastrointestinal fistula.

Prior/Concomitant Therapy

12. Has received prior therapy with lenvatinib, an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

    Note: Prior therapy with bevacizumab is not exclusionary.

13. Has received prior systemic anticancer therapy including investigational agents within 4 weeks before study treatment start.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy or ≤Grade 2 alopecia may be eligible.

14. Has not recovered adequately from the toxicity and/or complications from the intervention if participant received major surgical intervention before starting study treatment.

15. Has received prior radiotherapy within 2 weeks of start of study treatment. 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. Refer to Section 5.1.5 for GBM specific inclusion criteria.

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

17. Has known intolerance to lenvatinib (and/or any of the excipients).

Prior/Concurrent Clinical Study Experience

18. Has participated or is currently participating in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.

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

Diagnostic Assessments

19. Has urine protein ≥1 g/24h. Participants with proteinuria >1+ on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria.

20. Has prolongation of QTc interval (calculated using Fridericia's formula) to >480 ms.

    Note: If the QTcF is prolonged to >480 ms in the presence of a pacemaker, contact the Sponsor to determine eligibility.

21. Has left ventricular ejection fraction (LVEF) <55% as determined by multigated acquisition scan (MUGA) or echocardiogram (ECHO).

22. 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 intervention.

23. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression by imaging) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days before first dose of study intervention. GBM participants are exempt.

    Note: MRI brain scan will be conducted for all participants with stable brain metastases at screening. Brain CT scan should only be conducted when MRI is contraindicated.

24. Has tumors involving the brain stem.

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

26. 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.

27. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.

28. Has an active infection requiring systemic therapy.

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

30. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. (See Section 10.7 [Appendix 7] for country-specific requirements.)

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority. (See Section 10.7 [Appendix 7] for country-specific requirements.)

31. Has a known history of active tuberculosis (TB; Bacillus tuberculosis). (See Section 10.7 [Appendix 7] for country-specific requirements.)

32. 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.

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

Other Exclusions

34. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study intervention.

35. Has had an allogenic tissue/solid organ transplant (large organ transplants, stem-cell transplant requiring chronic immunosuppressant therapy necessary to prevent graft rejection).

5.2.1 GBM Specific Exclusion Criteria

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

36. Has carcinomatous meningitis.

37. Has recurrent tumor greater than 6 cm in maximum diameter.

38. Has tumor primarily localized to the brainstem or spinal cord.

39. Has presence of multifocal tumor, diffuse leptomeningeal or extracranial disease.

40. Has evidence of intratumoral or peritumoral hemorrhage on baseline MRI scan other than those that are ≤Grade 1 and either postoperative or stable on at least 2 consecutive MRI scans.

41. Has received Optune® TTFields within 2 weeks of study intervention.

The GBM participant will not be excluded from the study for systemic steroid therapy, as long as dexamethasone or its steroid equipotent dosing equivalent is administered as ≤2 mg by mouth daily and stable for a period of 5 days at the time of enrollment.

5.3 Lifestyle Considerations

No restrictions are required.

5.3.1 Contraception

Lenvatinib and pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

5.3.2 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with study intervention, the participant will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.5.

5.3.3 Use in Nursing Women

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention 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 (pembrolizumab and lenvatinib) 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 intervention(s) to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
Arm 1	Experimental	Lenvatinib	Drug	Capsule	10 mg, 4 mg[a]	20 mg	Oral	qd	Test Product	IMP	Central
Arm 1	Experimental	Pembrolizumab	Drug	Vial	25 mg/mL	200 mg	IV Infusion	q3w	Test Product	IMP	Central
Arm 2	Experimental	Lenvatinib	Drug	Capsule	10 mg, 4 mg	24 mg	Oral	qd	Test Product	IMP	Central

EEA = European Economic Area; IMP = investigational medicinal product; IV = intravenous; NIMP/AxMP = noninvestigational/auxiliary medicinal product; q3w = once every 3 weeks; qd = once daily.

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

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the pharmacy manual. Lenvatinib is a capsule for oral administration and does not require preparation.

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 the pharmacy manual for additional information.

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 in Cohorts A through G will be allocated to receive pembrolizumab + lenvatinib (Arm 1), with the following exception. The last approximately 60 participants in Cohort D will be assigned randomly in a 1:1 ratio to pembrolizumab + lenvatinib (Arm 1) or lenvatinib monotherapy (Arm 2).

6.3.2 Stratification

Participants will be stratified by tumor cohort and enrolled to receive study intervention with pembrolizumab + lenvatinib (Cohorts A-G) or lenvatinib monotherapy (Cohort D only).

6.3.3 Blinding

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

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.

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. Refer to Section 6.6.2 for dose modifications and toxicity management for AEs associated with lenvatinib; refer to Section 6.6.4 for other allowed dose interruption of lenvatinib.

6.5 Concomitant Therapy

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

Any medication (including over-the-counter medications) or therapy administered to the participant during the study (starting at the date of informed consent) will be recorded on the appropriate case report form (CRF). The investigator will record the AE for which the concomitant medication/therapy was administered on the appropriate CRF. If the

concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the appropriate CRF.

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study intervention and any concomitant therapy administered to the participant during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study intervention (or 90 days if used to treat an SAE) will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the participant's health and that is not expected to interfere with the evaluation of or interact with the study medication may be continued during the study.

See Section 10.7 (Appendix 7) for country-specific requirements.

6.5.1 Allowed Concomitant Medication(s)

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study medication. Antiemetic or any other prophylaxis should be considered in accordance with institutional guidelines.

The following concomitant medications are also allowed:

- Hormone replacement therapy
- Thyroid hormone suppressive therapy
- Anticoagulants including low molecular weight heparin, warfarin, anti-Xa agents
- Anti-inflammatory agents
- Bisphosphonates or denosumab
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the participant is enrolled)
- Palliative radiotherapy is permitted to a single lesion on an exceptional case by case basis after consultation with the Sponsor if considered medically necessary by the treating physician (for up to a maximum of 2 lesions). These lesions can NOT be a RECIST 1.1 or RANO-defined target lesion and the radiotherapy can NOT be administered for tumor control. Pembrolizumab should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study intervention; however, lenvatinib will be continued as planned during the palliative radiation.

Any additional procedural or participant-specific particularities should be discussed with the investigator and the Sponsor.

6.5.2 Prohibited Concomitant Medication(s)

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

- Concurrent anticancer therapies such as chemotherapy, targeted therapies (eg, tyrosine kinase inhibitors, Optune® TTFields [GBM cohort]), antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy not specified in this protocol

  Note: Topical anticancer agents to treat skin lesions (eg, in situ melanoma or squamous cell carcinoma) are allowed.

- Other concurrent investigational drugs.

- Live vaccines within 30 days and while participating in the study and within 90 days after last dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have immunologic etiology. Physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone equivalent may be used during the study.

  - Note: Inhaled steroids are allowed for management of asthma or seasonal allergies.

  - Note: Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

  - Note: Participants are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

  - Note: A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

  - Note: For the GBM cohort, the use of corticosteroids may be approved after consultation with the Sponsor. In the event pembrolizumab is held for corticosteroid use, pembrolizumab may not be restarted until participant is tolerating ≤2 mg dexamethasone (or equipotent dosing) for one week before restarting pembrolizumab and is clinically stable per investigator.

- Radiation Therapy

  Note: Radiation for pain or palliation may be acceptable (Section 6.5.1)

- Anticancer herbal supplements or alternative medicines are strongly discouraged during the Screening and Treatment Phase of this study.

If participants receive additional anticancer therapies, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These participants should complete all end-of-treatment assessments and continue to be followed for survival in the follow-up period.

6.5.3 Drug Interactions

A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A and P-gp substrate) were not altered in a clinically meaningful manner in the presence of lenvatinib. No significant DDI is therefore expected between lenvatinib and other CYP3A4/P-gp substrates.

Nonclinical studies identify CYP3A4 as the important CYP isozyme responsible for human hepatic metabolism of lenvatinib. However, clinical studies conducted showed that coadministration of lenvatinib with either inducers or inhibitors of CYP3A4/P-gp are not of clinical concern. Please refer to Appendix 8 and http://medicine.iupui.edu/flockhart/table.htm for the most current information.

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 (lenvatinib IB).

6.5.4 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. For participants receiving pembrolizumab + lenvatinib, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 3 in Section 6.6.1.1, along with the dose modification guidelines in Table 5 in Section 6.6.2. For participants receiving lenvatinib monotherapy, suggested supportive care measures and dose modification guidelines are outlined in Section 6.6.2.

Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder,

attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or lenvatinib.

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 3, Table 4, and Table 5 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification (Escalation/Titration/Other)

AEs will be graded using NCI CTCAE Version v4.0. For participants receiving combination therapy (Arm 1), 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 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.

6.6.1 Pembrolizumab

6.6.1.1 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. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 3.

See Section 10.7 (Appendix 7) for country-specific requirements.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

6.6.1.2 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 4.

Table 4 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 h	**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/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with: - Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). - Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: - Epinephrine** - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; PO=by mouth. Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v4.0 at http://ctep.cancer.gov		

6.6.1.3 Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record. Imaging should not be delayed for delays in cycle treatment.

6.6.2 Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib- or lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 5. An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.

The starting dose of lenvatinib is 20 mg/day for participants enrolled in the combination therapy arm (Arm 1). Lenvatinib dose reductions for Arm 1 occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the Sponsor.

The starting dose of lenvatinib is 24 mg/day for participants enrolled in the monotherapy arm (Arm 2). Lenvatinib dose reductions for Arm 2 will take place in succession based on the previous dose level (20, 14, and 10 mg/day). Any dose reduction below 10 mg/day must be discussed with the Sponsor.

For both Arm 1 and Arm 2, 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 (Table 5). For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.3.

See Section 10.7 (Appendix 7) for country-specific requirements.

Table 5 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	**Arm 1:** Reduce lenvatinib dose from 20 mg QD to 14 mg QD (1-level reduction) **Arm 2:** Reduce lenvatinib dose from 24 mg QD to 20 mg QD (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	**Arm 1:** Reduce lenvatinib dose from 14 mg QD to 10 mg QD (1-level reduction) **Arm 2:** Reduce lenvatinib dose from 20 mg QD to 14 mg QD (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	**Arm 1:** Reduce lenvatinib dose from 10 mg QD to 8 mg QD (1-level reduction) **Arm 2:** Reduce lenvatinib dose from 14 mg QD to 10 mg QD (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; QD=once daily.

Note: For grading see CTCAE version 4.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

a. An interruption of study treatment for more than 28 days will require Sponsor's approval before treatment can be resumed.
b. Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea 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 the 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 reach at least a 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. See Section 6.6.2.5.
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 v4.0, based on BP measurements only (and not on the number of antihypertensive medications).

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

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

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

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume 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 apart:

1. Continue study drug and institute antihypertensive therapy for participants not already receiving this.

2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.

3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

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

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

    - Additional dose reduction should be discussed with 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

See Section 10.7 (Appendix 7) for country-specific requirements.

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 testing or urinalysis per the SoA (Section 1.3). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine 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 urine protein-to-creatinine ratio [UPCR] test) is required in the following situations:

    - The first (initial) occurrence of ≥2+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while on study drug

    - 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 v4.0 will be based on the 24-hour urinary protein result if one has been obtained. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 5.

Monitoring:

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed on D15 (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 5 should be followed.

6.6.2.4 Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the SoA (Section 1.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure 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 5 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 (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 5 should be followed.

6.6.2.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v4.0, 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 5 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.

See Section 10.7 (Appendix 7) for country-specific requirements.

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 judgement 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 Q3W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

   - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

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

2. Severity of AE

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

3. Participants receiving the combination therapy (pembrolizumab + lenvatinib) 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 3, 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 >2 × ULN or INR >1.5)
  Although Table 3 advises pembrolizumab to be withheld (interrupted), and Table 5 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.

- For scheduled dental surgery or invasive dental procedures, stop lenvatinib for at least 1 week before the procedure, then restart lenvatinib when deemed clinically appropriate.

The reason for interruption should be documented in the participant's study record.

6.7 Intervention After the End of the Study

The study is complete upon consent of the last active treatment participant in an extension study using pembrolizumab monotherapy, coformulations, or in combination with a compound (eg, Lenvatinib), if available.

All study related procedures and data collection as defined per protocol will be terminated at study completion. In addition, survival follow-up will be stopped upon study completion as defined in Section 4.4.

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.

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 participate in the study as specified in Section 1.3 (SoA) and Section 8.10.4.

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 8.1.10.

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.

- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Sections 6.6.1, 6.6.2, and 6.6.4 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.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

- The participant has a positive serum or urine pregnancy test at any time during the course of the study.

- Initiation of a new anticancer treatment.

- Administrative reasons requiring cessation of treatment.

- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment. Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new nonulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy. Exceptions should be discussed with the Sponsor before continuing therapy or remaining in follow-up.

- Confirmed radiographic disease progression outlined in Section 8.2.1.5 or Section 8.2.1.6.

Note: Participants will be permitted to continue treatment beyond iRECIST- or RANO-defined progression (Arm 1 only) after confirming informed consent addendum has been documented and after Sponsor consultation.

- Unacceptable AE(s).

A participant may be discontinued from study intervention but continue to be monitored in the study for the following reason:

- PD as determined by the investigator.

  Note: Participants will be permitted to continue treatment beyond RECIST 1.1- or RANO-defined progression (Arm 1 only) as long as investigator-assessed clinical stability is observed, the participant is tolerating study intervention (Section 8.2.1.5 or Section 8.2.1.6) and after obtaining documented informed consent addendum. Treatment beyond confirmed PD per iRECIST or RANO may be permitted on Sponsor consultation.

Participants receiving the combination therapy (pembrolizumab + lenvatinib) 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

  Pembrolizumab will have already been permanently discontinued per Table 3 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)

Although Table 3 advises pembrolizumab to be withheld (interrupted), and Table 5 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both interventions must be permanently discontinued immediately.

Completion of pembrolizumab q3w consists of 35 treatments (approximately 2 years). Note: participants experiencing a clinical benefit, according to the PI, may continue on lenvatinib beyond this time point with Sponsor consultation. Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of lenvatinib beyond the date when the initial CR was declared.

7.2 Participant Withdrawal From the Study

It has been well-documented that a higher rate of withdrawal can render a study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

As clinical event data are important study endpoints, participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue all remaining study visits for follow-up and vital status assessment as outlined in the SoA and Section 8.10.4.

The investigator is to inform the participants that:

- they may discontinue from study intervention at any time during the study, and
- they are encouraged to continue visits in the study for follow-up, imaging, and vital status assessment.

If participants elect to stop study procedures, they are encouraged to continue to be followed, which allows periodic survival follow-up and vital status data to be collected.

If a participant fails to return for scheduled visits and/or if the study site is unable to contact the participant after multiple attempts (ie, is lost to follow-up), the procedures to be performed are outlined in Section 7.3.

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

Participants who withdraw consent during the study

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

Section 8.1.10 delineates the specific procedures performed at the time of withdrawal.

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last

known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

- 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.

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 Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or 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 will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Disease-specific Biomarker Data Collection

Where available, the following will be collected:

Cohort	Biomarker
GBM	Isocitrate dehydrogenase 1 Isocitrate dehydrogenase 2 MGMT PD-L1
CRC	Microsatellite instability Mismatch repair BRAF RAS Epidermal growth factor receptor TMB PD-L1
Gastric	Microsatellite instability Mismatch repair PD-L1 Human epidermal growth factor receptor 2/neu
Biliary	None
Ovarian	BRCA 1 BRCA 2
TNBC	BRCA 1 BRCA 2
Pancreatic	BRCA 1 BRCA 2 Microsatellite instability Mismatch repair

BRAF = proto-oncogene B-Raf; BRCA = breast cancer susceptibility gene; MGMT = O-6-methylguanine-DNA methyltransferase; PD-L1 = programmed cell death ligand 1; RAS = Rat Sarcoma Viral Oncogene Homolog; TMB = tumor mutational burden.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 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 Cycle 1 Day 1.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Concomitant medications will be recorded for 30 days after the last dose (or for up to 90 days for SAEs).

8.1.7 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 allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be nonrandomly allocated and will receive a treatment number. The treatment number identifies the participant for all procedures occurring after treatment. Once a treatment number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.9 Study Intervention Administration

Pembrolizumab will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

Study intervention should begin within 3 days of allocation/randomization.

Lenvatinib may be administered at home, except on Day 1 of Cycles 1 and 2 (required clinic visit for ECG testing, per SoA) and on Day 15 of Cycle 1 (lenvatinib PK sample collection, per SoA), for participants in Arm 1 only. Please refer to Section 8.1.9.1.1 for further details.

8.1.9.1 Timing of Dose Administration

8.1.9.1.1 Lenvatinib

Lenvatinib is provided as 4 mg or 10 mg capsules. Lenvatinib 20 mg (Arm 1) or 24 mg (Arm 2) once daily will be taken orally with water (with or without food) at approximately the same time each day in each 21-day cycle. However, for participants in Arm 1, lenvatinib

will be administered 0 to 4 hours after completion of pembrolizumab administration on Day 1 of Cycles 1 and 2.

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

8.1.9.1.2 Pembrolizumab

Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: –5 minutes/ +10 minutes).

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

8.1.9.2 Compliance

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 Discontinuation and Withdrawal

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the End of Treatment Visit at the time of withdrawal.

If discontinuation occurs ≥30 days after the last dose of study treatment, a Safety Follow-up Visit (Section 8.10.4.1) is not required. In this situation, all procedures required at the 30-day Safety Follow-up Visit and end of treatment (EOT) Visit are performed once and entered into the EOT Visit only.

8.1.11 Participant Blinding/Unblinding

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

8.1.12 Calibration of Equipment

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

8.1.13 Antineoplastic Treatment

The investigator or qualified designee will review all new antineoplastic treatment initiated after the last dose of study treatment. Once new antineoplastic treatment has been initiated, the participant will move into survival follow-up. All antineoplastic treatment will be recorded until time of death or termination of survival follow-up. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image acquisition, collection and transmission to the iCRO can be found in the Site Imaging Manual (SIM). Sites should follow the image acquisition guidelines described in the SIM to acquire diagnostic quality images. For cohorts other than GBM, tumor imaging of chest, abdomen and pelvis is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. For GBM, an industry-standard brain tumor imaging protocol will be used [Ellingson, B. M.,Bendszus, M., et al 2015] (see SIM). For breast cancer, nuclear medicine bone scan should be performed at screening, and if bone metastases are present, every 27 weeks, or more often if clinically indicated. If CR is suspected based on anatomic imaging, a bone scan is required to confirm clearance of bone metastases either within the same imaging visit as the anatomic imaging, or on the next anatomic scan. For ovarian cancer, CT oral contrast must be used besides the use of IV contrast (see SIM).

The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Expedited confirmation of measurable disease based on RECIST 1.1 (or RANO for GBM) by BICR at Screening will be used to determine participant eligibility. Confirmation by BICR that the participant’s imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 (or RANO for GBM) is required before participant allocation.

All scheduled images for all study participants from the sites will be submitted to the BICR. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which shows radiologic progression, should also be submitted to the iCRO.

When the investigator identifies radiographic progression per RECIST 1.1, but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the BICR until the start of new anticancer therapy, death, or withdrawal of consent.

8.2.1.1 Initial Tumor Imaging

The screening images must be submitted to the iCRO for confirmation of measurable disease per RECIST 1.1 (or RANO for GBM) for eligibility before allocation.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days before the date of first dose and can be assessed by the iCRO.

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

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment for all cohorts (except GBM) should be performed at 9 weeks (63 days ±7 days) from the date of treatment initiation. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed q24w, or sooner if clinically indicated.

For participants with GBM, the first on-study imaging assessment should be performed at 6 weeks (42 days to 49 days) from the date of treatment initiation. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) until Week 18 and then every 9 weeks thereafter or more frequently if clinical indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed q24w, or sooner if clinically indicated.

Imaging timing should follow calendar days from treatment initiation and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the iCRO.

For participants with GBM, brain MRI is required at baseline and all time points for efficacy assessments. For non-GBM cohorts, participants with previously treated brain metastases are required to have a brain MRI at screening and at all subsequent tumor assessment time points. A brain MRI is also required for all participants when clinically indicated.

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

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

Per iRECIST (Section 8.2.1.5), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 8.2.1.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 8.2.1.5.

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

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

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

8.2.1.4 RECIST 1.1 Assessment of Disease (Non-GBM Cohorts)

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.

8.2.1.5 iRECIST Assessment of Disease

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

Clinical stability is defined as the following:

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

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

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

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 9, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor and after obtaining signed informed consent addendum. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the iCRO.

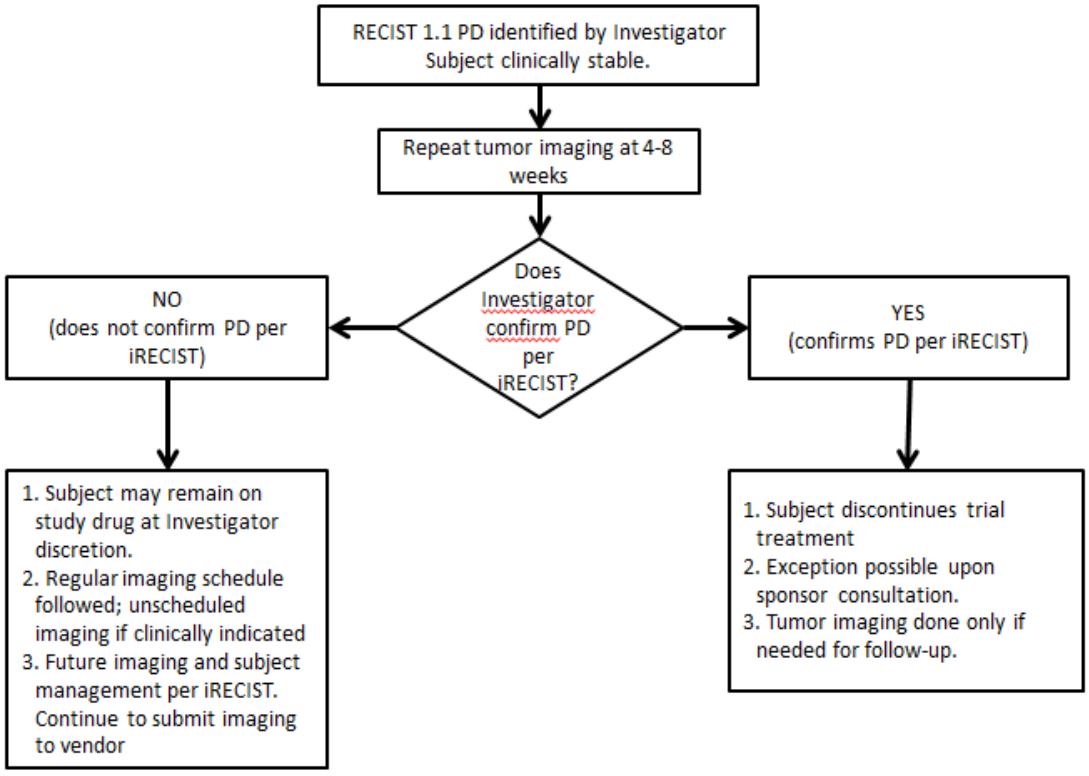
A description of the adaptations and iRECIST process is provided in Appendix 9, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated as a flowchart in Figure 2.

Table 6 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1.	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study intervention at the investigator's discretion and after the participant's consent.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment (exception is possible on consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure 2 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator



iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for Immune-Based Therapeutics; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors.

8.2.1.6 Response Assessment in Neuro-Oncology (RANO)

RANO criteria have been the preferred criteria for assessing responses in GBM studies since their publication in 2010 [Wen, P. Y., et al 2010] and incorporate measurements of tumor size as shown in contrast-enhanced MRI with qualitative assessment of both enhancing and nonenhancing disease, and information on steroid dosing and participant functional performance status. Response assessments will be performed by investigators and by BICR. RANO also makes provisions for the pseudoprogression frequently seen after radiotherapy. The implementation of RANO is described in detail in Appendix 10, and in the iCRO imaging charter.

If disease progression is established by the investigator, the process continues as follows:

- Participants will be permitted to continue treatment as long as investigator-assessed clinical stability is observed, the participant is tolerating study intervention and after obtaining documented informed consent addendum.

- If the participant continues treatment, the tumor imaging for confirmation of progression may be performed at the earliest 4 weeks after the first indication of progression, or at the next scheduled scan, whichever is clinically indicated. All scans are to be sent to the iCRO.

- Treatment beyond confirmed PD may be permitted on Sponsor consultation.

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

- unacceptable toxicity

- clinical signs or symptoms indicating clinically significant disease progression

- decline in performance status

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

8.2.2 Patient-reported Outcomes

Health-related QoL will be assessed at Cycle 1 Day 1 (before the first dose of study intervention), every cycle through Cycle 13, Cycle 17, Cycle 21, at the time of discontinuation (EOT Visit), and the 30-day Safety Follow-up Visit (See SoA in Section 1.3 for electronic patient-reported outcomes [ePRO] administration schedule). If the EOT Visit occurs 30 days from the last dose of study treatment, a Safety Follow-up Visit is not required, ePROs do not need to be repeated.

HRQoL questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 first, then the cohort-specific ePROs listed below, and EuroQoL EQ-5D last:

- Breast (QLQ-BR23)

- Ovarian (QLQ-OV28)

- Gastric (QLQ-STO22)

- Colorectal (QLQ-CR29)

- GBM (QLQ-BN20)

- Biliary (QLQ-BIL21)

- Pancreatic (QLQ-PAN26)

It is best practice and strongly recommended that electronic patient-reported outcomes (ePROs) are administered to allocated 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.

If at the time of enrollment of a participant, the translated version of any PRO measure is not available for that language/country, and therefore cannot be completed by the participant at Cycle 1 Day 1, then the PRO measure will not be required for this participant at any point during the study. The other study PRO measures must be completed as scheduled.

NOTE: For some sites, the translated PRO measure might become available after study startup and should be administered to participants at their time of enrollment; for some sites, the PRO measure translation might not be available for the entire duration of the study.

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 laboratory manual.

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

8.3.1 Physical Examinations

Physical examinations (full physical or symptom-directed) including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination including oral examination during Screening. 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. Height and weight will also be measured and recorded.

8.3.1.2 Symptom-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 before the administration of the study intervention. A symptom-directed physical examination may be performed at any time during the study, as clinically indicated. New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

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

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

Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BR <90 mm Hg. If the participant's initial BP measurement 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.

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 investigator/site may provide a diary as a tool to aid the participant in collecting BP evaluations between clinic visits. The Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP retest, or other clinically appropriate intervention(s).

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 before the ECG. The Fridericia correction method for calculating QTc will be used.

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

QTc prolongation has been seen in some lenvatinib studies. Monitor ECGs every cycle (as specified in the SoA) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QTc 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 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 on institutional reports.

8.3.5 Child-Pugh Score

Originally developed in 1973, the Child-Pugh score was used to estimate the risk of operative mortality in patients with bleeding esophageal varices. It has since been modified, refined, and become a widely used tool to assess prognosis in patients with chronic liver disease and cirrhosis. The score considers 5 factors, 3 of which assess the synthetic function of the liver (ie, Tbil level, serum albumin, and coagulation parameters [INR or PT]) and 2 of which are based on clinical assessment (ie, degree of ascites and degree of hepatic encephalopathy).

A total Child-Pugh score of 5 to 6 is considered Child-Pugh Class A (well-compensated disease); 7 to 9 is Class B (significant functional compromise); and 10 to 15 is Class C (decompensated disease). These classes correlate with one- and two-year patient survival: Class A: 100 and 85%; Class B: 80 and 60%; and Class C: 45 and 35%.

The BTC cohort will include participants only with a Class A Child-Pugh score.

8.3.6 Clinical Safety Laboratory Assessments

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

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

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days 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.

8.3.6.1 Laboratory Safety Assessments

Hematology, clinical chemistry, routine urinalysis and other laboratory safety assessments are specified in Appendix 2 and will be performed according to the SoA.

The results of laboratory safety assessments scheduled before the administration of study intervention must be reviewed before the 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 treatment.

8.3.6.2 Urine Dipstick

Urine dipstick testing will be performed locally within 7 days before the start of treatment. Participants with >1+ 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.

Once participants are allocated, urine dipstick testing for participants with proteinuria ≥2+ should be performed until the results have been 1+ or negative for 2 consecutive treatment cycles. Urine dipstick testing should be performed at the investigational site. If a new event of proteinuria ≥2+ occurs, the participant must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 2 consecutive treatment cycles.

For participants with proteinuria ≥2+, see Section 6.6.2.2.

8.3.7 Eastern Cooperative Oncology Group Performance Status

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 status within 3 days of allocation/randomization, before the administration of each cycle of study intervention, and during the follow-up period, as specified in the SoA (Section 1.3).

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event 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 allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

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

- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following pembrolizumab or 30 days following cessation of lenvatinib, whichever occurs last, must be reported by the investigator. If the participant initiates new anticancer therapy following discontinuation of study intervention, the time period for reporting pregnancies and exposure during breastfeeding is reduced to 30 days following cessation of study intervention.

- 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.

Participants who enter the Extension Study:

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

Note: Once consented to the extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

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

Table 7 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:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (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 wth 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study is 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. Any suspected endpoint that on review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

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

8.5 Treatment of Overdose

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

- Pembrolizumab: ≥5 times the protocol-specified dose
- Lenvatinib: any dose above the protocol-specified dose if associated with an AE

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients 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 and RCC.

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

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.”

8.6 Pharmacokinetics

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

To evaluate the immunogenicity and exposure of pembrolizumab in these indications, blood samples for PK and antidrug antibodies will be collected and may be stored only at this time. Further analysis may be performed if required and reported separately if conducted.

Blood samples will be collected from all participants. Plasma concentrations of lenvatinib when coadministered with pembrolizumab will be measured. Lenvatinib will be analyzed using a population PK approach.

Lenvatinib will be quantified by use of validated High-Performance Liquid Chromatography -tandem mass spectroscopy method.

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 as specified in the SoA:

- Blood for serum biomarkers
- Blood for genetic analysis
- Blood for RNA analysis
- Blood for plasma biomarkers
- Blood for circulating tumor nucleic acids
- Tumor blocks or slides

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

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Health Economics Medical Resource Utilization and Health Economics

Medical resource use 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 room visits must be reported in the eCRF, from the time of treatment allocation/randomization through 90 days after cessation of study intervention, or 30 days after cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.10 Visit Requirements

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

8.10.1 Screening

Written consent must be obtained before performing any protocol-specific procedure. Results of a test performed before the participant providing documented 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 before the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 7 days before the first dose of study intervention. An exception is Hepatitis testing which may be performed up to 28 days before the first dose of study intervention.

- Evaluation of ECOG performance status is to be performed within 3 days before allocation/randomization.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours before the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Tumor tissue must have been obtained before allocation.

8.10.2 Rescreening

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.

8.10.3 Treatment Period

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

8.10.3.1 Phone 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).

8.10.4 Post treatment Visit

8.10.4.1 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 EOT Visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at the 30-day Safety Visit and EOT are performed once and entered into the EOT Visit only.

8.10.4.2 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 move into the Efficacy Follow-up Phase and should be assessed according to the same imaging schedule used while on treatment. Calculated from the date of first dose, imaging should be performed every 9 weeks (63 days ±7 days), or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants will have imaging performed every 12 weeks (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed every 24 weeks, or sooner if clinically indicated, to monitor disease status. For participants with GBM, imaging to be performed at 6 weeks (42 days to 49 days) from the date of treatment initiation. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) until Week 18 and then every 9 weeks thereafter or more frequently if clinical indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days) or sooner if clinically indicated until Week 102. After Week 102, imaging should be performed q24w, or sooner if clinically indicated. Imaging timing should follow calendar days from treatment initiation. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

If a clinic visit is not feasible, the participant may be contacted by telephone or email. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants will also be asked to complete HRQoL questionnaires as outlined in Section 8.2.2.

All participants who discontinue study intervention before disease progression will continue to undergo tumor assessments in the imaging follow-up phase until disease progression or a new anticancer therapy is initiated, unless the participant withdraws consent.

8.10.4.3 Survival Follow-up Assessments

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

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

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

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

8.10.5 Survival Status

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

9 STATISTICAL ANALYSIS PLAN

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

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Multicenter, Open-label Phase 2 Study of Lenvatinib (E7080/MK-7902) Plus Pembrolizumab (MK-3475) in Previously Treated Subjects with Selected Solid Tumors (LEAP-005)
Treatment Assignment	Pembrolizumab 200 mg q3w and Lenvatinib 20 mg qd Lenvatinib 24 mg qd
Analysis Populations	Efficacy and Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	1) OR per RECIST 1.1 or RANO (GBM) by investigator assessments in initial cohorts and by BICR in cohorts that expand combining the initial and expansion cohorts (Cohorts A-F). For Cohort G, OR per RECIST 1.1 by BICR assessment. 2) Safety

Key Secondary Endpoints	3) Disease control 4) DOR 5) PFS 6) OS
Statistical Methods for Key Efficacy Analysis	The point estimate and exact Clopper-Pearson confidence interval (CI) will be provided for ORR.
Statistical Methods for Key Safety Analyses	Safety will be evaluated using descriptive statistics.
Interim Analyses	For Cohorts A-F, interim analyses, based on investigator assessments of efficacy, will be performed when the first 30 participants within a tumor cohort have been followed up for approximately 6 months from study entry. The results of each IA will be reviewed by the Sponsor, and recommendations for cohort expansion will be provided. For Cohort G, an IA will be performed when the first 30 participants enrolled have been followed up approximately 6 months. The results will be reviewed by the Sponsor, and recommendations to stop or continue enrollment will be provided.
Multiplicity	No multiplicity adjustment is planned
Sample Size and Power	Cohorts A-F: Approximately 180 participants will be enrolled in the study initially; that is, 30 participants per tumor type. Based on the interim analysis, the sample size for Cohorts A, B, C, E and F may be increased to a total of 100 participants to receive pembrolizumab + lenvatinib (Arm 1). After the IA, Cohorts A (TNBC) and B (ovarian cancer) discontinued enrollment. Based on the IA, the sample size for Cohort D (CRC) may be increased to a total of 130 participants, with the first 40 after initial 30 (total 70) participants to receive pembrolizumab + lenvatinib (Arm 1) and the last 60 participants in Cohort D randomized in a 1:1 ratio to receive pembrolizumab + lenvatinib (Arm 1) or lenvatinib monotherapy (Arm 2). Cohort G will enroll a maximum of 100 participants to receive pembrolizumab + lenvatinib.

9.2 Responsibility for Analyses/In-house Blinding

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

This study is being conducted as an open-label study, ie, 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. Independent radiologist(s) will perform the central imaging review without knowledge of participant-level treatment status.

For Cohort D (CRC), the last 60 participants will be randomized in a 1:1 ratio between Arm 1 and Arm 2. The Sponsor will generate the randomized allocation schedule(s) for study intervention assignment for this protocol, and the randomization will be implemented in IRT.

9.3 Hypotheses/Estimation

The objectives of the study are stated in Section 3. There is no formal hypothesis for this open-label study.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

The primary efficacy endpoint is OR. For Cohorts A-F, response for the primary analysis will be determined by investigator assessments in initial cohorts and by BICR in cohorts that expand (combining the initial and expansion cohorts), with confirmatory assessment as required per RECIST 1.1 and RANO. For Cohort G, response for the primary analysis will be determined by BICR, with confirmatory assessment as required per RECIST 1.1. The ORR, defined as the proportion of participants who have a best overall response of either CR or PR using RECIST 1.1 (or RANO for GBM participants) at any time during the study, will be analyzed. Participants with unknown or missing response information will be treated as nonresponders.

Secondary Efficacy Endpoints

1. Disease control, defined as the best overall response of CR, PR, or stable disease based on RECIST 1.1.

2. DOR, defined in the subset of participants with a CR or PR, based on RECIST 1.1 (or RANO for GBM participants), as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause, whichever occurs first.

3. PFS, defined as the time from date of study treatment to the first documented disease progression based on RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ (or RANO for GBM participants) or death due to any cause, whichever occurs first.

4. OS, defined as the time from the date of study treatment to the date of death due to any cause.

OR, DCR, DOR, and PFS based on iRECIST by investigator assessment are exploratory endpoints in participants who received pembrolizumab + lenvatinib combination therapy. The details on these exploratory endpoints will be provided in the supplemental SAP.

9.4.2 Safety Endpoints

A description of safety endpoint assessment is provided in Section 4.2.3.2.

The primary safety endpoints are treatment-emergent AEs, serious AEs, and discontinuation due to AEs. The AEs are graded using NCI CTCAE (Version 4.0).

Other safety endpoints include laboratory safety assessment and vital signs.

9.4.3 Patient-reported Outcome Endpoints

The PRO endpoints are based on the following questionnaires:

- EORTC QLQ-C30
- EORTC-QoL-disease-specific
  - Breast (QLQ-BR23)
  - Ovarian (QLQ-OV28)
  - Gastric (QLQ-STO22)
  - Colorectal (QLQ-CR29)
  - GBM (QLQ-BN20)
  - Biliary (QLQ-BIL21)
  - Pancreatic (QLQ-PAN26)
- EQ-5D-5L

The multi-item scales and single items (as introduced in Section 4.2.3.3) on EORTC QLQ-C30, disease-specific EORTC instruments, and on EQ-5D-5L will be summarized. The scoring algorithm of the multi-item scale(s) for each instrument will be provided in the sSAP. TTD will be evaluated for EORTC QLQ-C30 scales. Data will be summarized for pre-specified time points. Details will be provided in the sSAP.

9.5 Analysis Populations

Participants are enrolled/randomized in the study when they have received an allocation number via IRT (Section 6.3.1).

The efficacy and safety analyses populations will be defined for each tumor cohort.

9.5.1 Efficacy Analysis Populations

Efficacy Analyses will be conducted in the APaT population, which consists of all enrolled/randomized participants who received at least 1 dose of study intervention (pembrolizumab + lenvatinib combination therapy or lenvatinib monotherapy).

For the evaluation of the efficacy of pembrolizumab + lenvatinib combination therapy and lenvatinib monotherapy, the analysis population will be based on all treated participants that are allocated to the corresponding treatment arm.

The evaluation of the efficacy of the combination therapy relative to the lenvatinib monotherapy will include all treated participants from the randomized subcohort.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all enrolled/randomized participants who received at least 1 dose of study intervention (pembrolizumab + lenvatinib combination therapy or lenvatinib monotherapy).

In the APaT population for safety analysis, participants will be included in the treatment arm corresponding to the study intervention that they actually received. For most participants, this will be the treatment arm to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment arm corresponding to the study intervention actually received.

At least 1 laboratory, vital sign, or ECG measurement obtained after at least 1 dose of study intervention 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 Population

The PRO analyses are based on the PRO Per Protocol Treated (PRO PPT) population, defined as all allocated participants who have PRO assessments available at both baseline and the specified postbaseline timepoint for the specific endpoint and have received at least one dose of the study intervention.

9.6 Statistical Methods

Both efficacy and safety analyses will be assessed by arm within each cohort.

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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, vital signs, and ECG measurements. All safety analyses will be performed in the APaT population by treatment arm within each cohort.

Adverse Events

Events will be summarized based on number and proportion of total participants by system organ class and preferred term. Separate summaries with descriptive statistics (counts and percentage) will be given for all AEs, treatment-related AEs, AEs by toxicity grade, SAEs and AEs leading to discontinuation of study intervention and dose modification.

ECIs will be identified and additional summaries provided.

The incidence of deaths and the primary cause of death will be summarized.

Further details on the statistical approach of safety analysis will be described in the sSAP.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics will be assessed by the use of tables and/or graphs. The number and percentage of participants screened and enrolled/randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment arm either by descriptive statistics or categorical tables.

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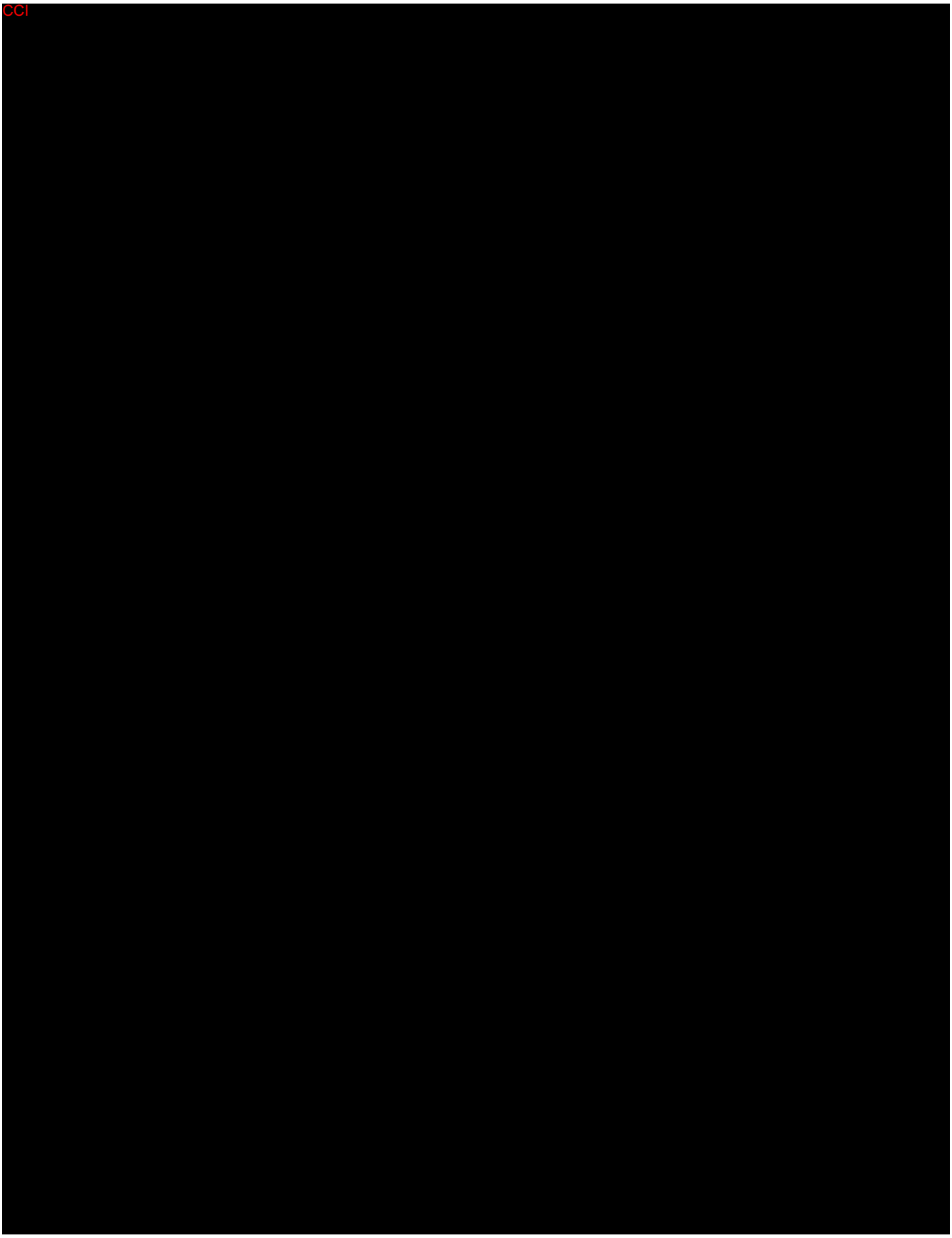

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9.8 Multiplicity

There will be no hypothesis testing performed in this study. For the primary and secondary objectives in this Phase 2 study, no adjustment to control for Type I error is planned.

9.9 Sample Size and Power Calculations

The study will initially enroll 30 participants per cohort in Cohorts A-F. Based on the IA, 70 additional participants may be enrolled in Cohorts A, B, C, E and F to receive pembrolizumab + lenvatinib combination therapy. However, after IA, Cohorts A (TNBC) and B (ovarian cancer) discontinued enrollment.

Based on the IA, 100 additional participants may be enrolled in Cohort D. The first 70 participants will receive pembrolizumab + lenvatinib combination therapy and the last approximately 60 participants will be randomized in a 1:1 ratio to either pembrolizumab + lenvatinib combination therapy (Arm 1) or lenvatinib monotherapy (Arm 2). Additionally, up to 100 participants will be enrolled in Cohort G. Table 11 shows the CIs when N=30 and N=100, given different numbers of responders. Table 12 shows the true ORR required to achieve at least 80% probability that the exact 95% CI of ORR is above historical ORR/current therapies.

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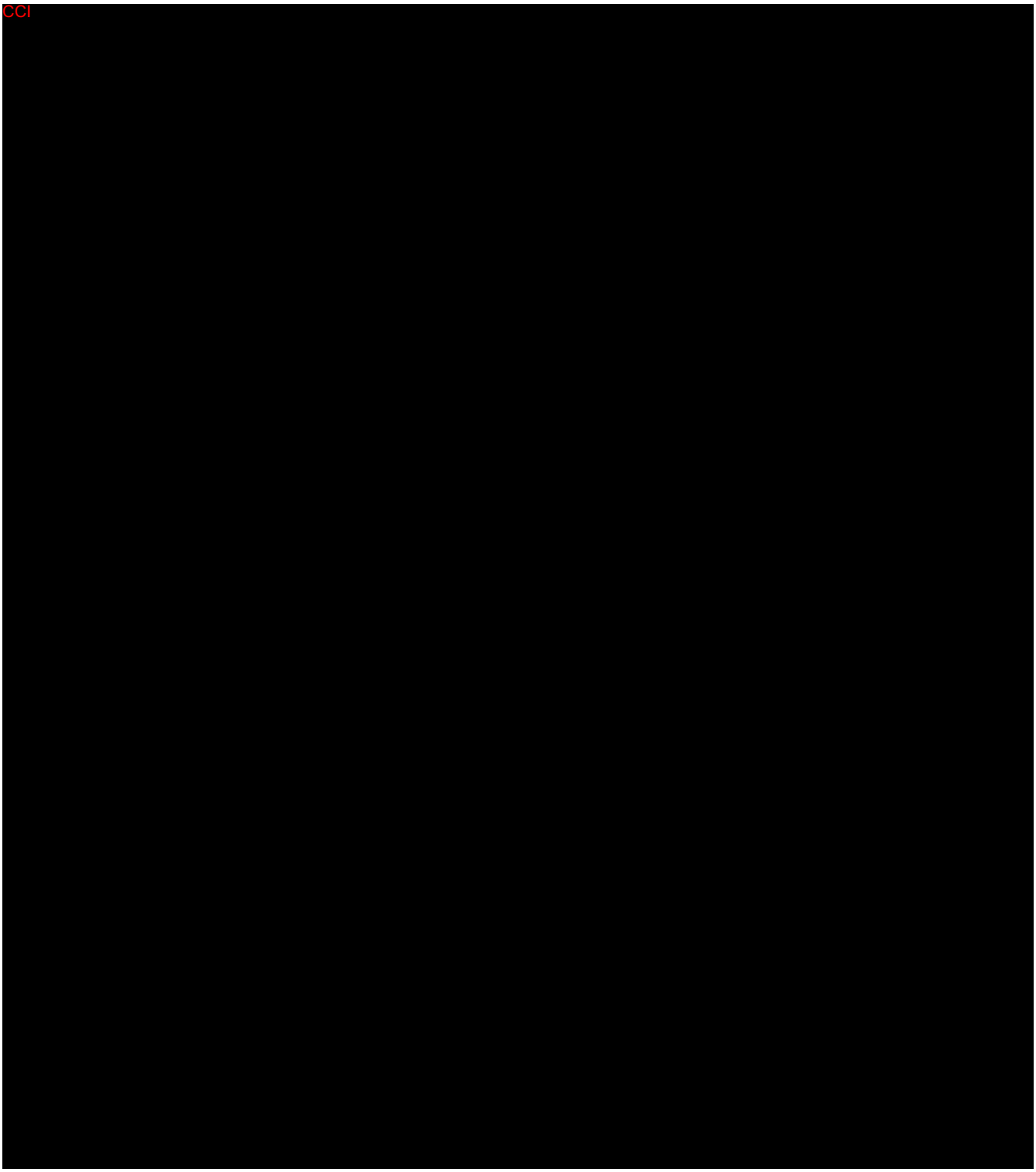

9.10 Subgroup Analyses

If data warrant, subgroup analysis will be performed for participants receiving pembrolizumab + lenvatinib combination therapy in cohorts with enrollment expansion and Cohort G if the full enrollment of 100 participants occurs:

- Gender (except ovarian cancer)
- Race
- Age (<65, ≥65)
- Exploratory analysis may be performed for subgroups defined by biomarkers (eg, PD-L1 expression).

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 number of cycles and days in which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the APaT population for each arm.

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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF 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 Scientific Advisory Committee (SAC)

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use 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 Studies.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 15 will be performed by the local laboratory.

Clinical laboratory assessments may be conducted any time within 72 hours before the scheduled visit, unless otherwise specified. Procedures/assessments should be performed before administration of study treatment.

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.

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 5.1 and Section 8.10.1.
- All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours of the first dose of study intervention
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 15 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	Blood Urea Nitrogen (BUN)[c]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine[d]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic Pyruvic Transaminase (SGPT)	Total Protein
	Glucose nonfasting	Calcium	Alkaline phosphatase	Magnesium
	Amylase	Lipase		
	Lactate dehydrogenase			
Routine Urinalysis/Urine dipstick testing[e]	• Specific gravity • pH, glucose, protein[f,g], blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Laboratory Tests	• Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) • Serology (HIV antibody, Hepatitis B surface antigen [HBsAg], and Hepatitis C virus antibody) • Thyroid-stimulating hormone (TSH), Free thyroxine (FT4), Triiodothyronine (T3)[h] • INR or PT, aPTT[i] and Fibrinogen[i]			

aPTT = activated partial thromboplastin time; C1 = cycle 1; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell (count); T3 = triiodothyronine; T4 = tetraiodothyronine; TSH = thyroid-stimulating hormone; WBC = white blood cell (count); WOCBP = woman of childbearing 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. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine
e. If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory
f. If urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection or an immediate spot urine protein-to-creatinine (UPCR) test should be performed to quantify the 24-hour urine protein excretion. 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.
g. Participants with >1+ 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.
h. Free T4, T3, and TSH levels will be performed during screening and then repeated on Day 1 of every other cycle (starting Cycle 2), at the time of discontinuation (end of treatment), and at the Safety-Follow-up visit. Free T3 is acceptable where T3 cannot be determined. There may be instances when sites are unable to obtain thyroid function testing results before the scheduled dosing. After C1, review of thyroid function test results after dosing is acceptable.
i. Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulation therapy

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

See Section 10.7 (Appendix 7) for country-specific requirements.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, 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." Lenvatinib overdose without an associated adverse event is not reportable as an AE. Refer to Section 8.5 for the definition of overdose.

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.

Assessment of causality

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

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 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 follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom cannot be used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

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

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

After initiation of treatment additional pregnancy testing will be performed every 30 days during the treatment period and 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first, and as required locally.

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

See Section 10.7 (Appendix 7) for country-specific requirements.

10.6 Appendix 6: NYHA Criteria

The NYHA Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac participants. On the basis of NYHA definitions, participants are to be classified as follows:

Class	**Definition**
Class I	Participants with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Participants with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Participants with marked limitation of activity; they are comfortable only at rest.
Class IV	Participants who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Adapted from The Criteria Committee of the New York Heart Association, 1994 [Dolgin, M., et al 1994] [Dolgin, M., et al 1994a].

10.7 Appendix 7: Country-specific Requirements

10.7.1 France

Section 5.1 Inclusion Criteria

13. Adequately controlled BP with or without antihypertensive medications, defined as BP ≤140/90 mm Hg at Screening and no change in antihypertensive medications within 1 week before C1D1.

Section 6.5 Concomitant Therapy

Drugs known to prolong the QTc interval must be used cautiously. Please refer to https://www.crediblemeds.org for a list of QTc prolonging medications.

Section 6.6.1.1 Dose Modification and Toxicity Management for Immune-related AEs Associated With Pembrolizumab

Participants should be discontinued from study treatment if any of the following AEs occur:

- Recurrent Grade 3 colitis
- Grade 4 rash
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Please refer to the current pembrolizumab Summary of Product Characteristics (SmPC) for additional guidance on management of immune-related AEs associated with pembrolizumab.

Please refer to the current lenvatinib SmPC for additional guidance on management of AEs associated with lenvatinib administration and other contraindications.

Section 6.6.2 Lenvatinib (Dose Modification)

Per the SmPC for lenvatinib, please note the increased risk of QT prolongation especially in patients with resting heart rates less than 50 bpm.

Hypomagnesemia

Serum magnesium should be monitored per the SoA (Section 1.3). Hypomagnesemia should be treated per institutional guidelines.

Hypokalemia

Serum potassium should be monitored per the SoA (Section 1.3). Hypokalemia should be treated per institutional guidelines.

Section 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 ≤140/90 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.

10.7.2 Germany

Section 1.3 Schedule of Activities

SAEs will be monitored for 120 days after the last dose of study intervention.

Pregnancy testing will be continued for 120 days after the last dose of study intervention, regardless of initiation of subsequent anticancer therapy.

Section 5.2 Exclusion Criteria

- Has a known history of HIV infection. HIV testing is required at Screening.
- Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for Hepatitis B or Hepatitis C is required at Screening.
- Has a known history of active tuberculosis (TB; Bacillus tuberculosis). Testing for tuberculosis is required at Screening.

Section 10.2 Appendix 2: Clinical Laboratory Tests

- Other screening tests: tuberculosis

10.7.3 United Kingdom

Section 1.3 Scheduled of Activities / Section 10.5.3 Pregnancy Testing

A pregnancy test is required every cycle for WOCBP, and if urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

Section 6.5 Concomitant Therapy

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

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.

10.7.4 Canada

Please refer to the current lenvatinib product monograph for management of AEs associated with lenvatinib administration.

Section 5.1 Inclusion Criteria

13. Have adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no change in antihypertensive medications within 1 week before randomization.

    Note: Eligibility of a participant receiving ≥3 antihypertensive medications before study entry will require consultation with the Sponsor.

Section 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 3 fistula.

10.7.5 Argentina

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

Section 1.3 Schedule of Activities - Screening and Treatment Phase

Pregnancy testing must be performed at each cycle during treatment as well as at the end of study treatment.

Section 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Pregnancy testing must be performed at each cycle during treatment as well as at the end of study treatment.

10.8 Appendix 8: Clinical Studies Evaluating Drug-Drug Interactions With Lenvatinib

Nonclinical studies identify CYP3A4 as a potentially important Cytochrome P450 isozyme responsible for metabolism of lenvatinib. Clinical studies were conducted to test these findings.

Simultaneous CYP3A4/P-glycoprotein (P-gp) inhibition by ketoconazole slightly (15% to 19%) increases systemic exposure to lenvatinib [Shumaker, R., et al 2015]. Since no change was observed in half-life, T_{max}, or lag time (T_{lag}), the slight increase in systemic exposure is probably related to a decrease in first pass metabolism. However, since the magnitude of change is small, coadministration of lenvatinib with CYP3A4/P-gp inhibitors is not of clinical concern.

The influence of P-gp inhibition on lenvatinib PK has been investigated. P gp inhibition was accomplished by coadministering a single dose of rifampin with a single dose of lenvatinib. Preliminary results suggest P-gp inhibition increases systemic exposure to lenvatinib 26% to 32%. Thus, coadministration of lenvatinib with P-gp inhibitors only causes a small increase in lenvatinib exposure.

The influence of simultaneous P-gp and CYP3A4 induction on lenvatinib PK has been investigated. Examination of simultaneous P-gp and CYP3A4 induction on lenvatinib PK was accomplished by administering rifampin qd for 21 days [Shumaker, R. C., et al 2014]. A single dose of lenvatinib was coadministered with the 15th dose of rifampin. Based on preliminary data, simultaneous P-gp and CYP3A4 induction minimally altered lenvatinib exposure as mean C_{max} increased about 8% while the area under the concentration-time curve (AUC) decreased about 7% coadministration of lenvatinib with CYP3A4/P-gp inducers is not of clinical concern.

The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and nonenzymatic processes (Lenvima® Package Insert).

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

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management (see Table 6 and Figure 2). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit , an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudo-progression Resolves

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

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

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

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

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

10.10 Appendix 10: Response Assessment in Neuro-Oncology (RANO) Response Criteria

Treatment response assessment will be based on the RANO criteria (Wen 2010), using a combination of clinical and imaging data. At baseline, tumor burden is documented by selection of lesions that will be followed quantitatively (target lesions) and qualitatively (nontarget). At each visit afterward, imaging assessment consists of evaluating target and nontarget lesions, searching for new lesions, and review of the abnormalities on T2/FLAIR images. These assessments are combined into a radiographic response, which is then combined with clinical performance status and steroid dose information to determine the overall response for each visit. Endpoint information, such as the best overall response, is determined from the sequence of visit responses as described in the SAP.

Scan acquisition

Imaging will be acquired using the standardized brain tumor imaging protocol (Ellingson 2015). It will include pre- and post-contrast T1-weighted MRI, as well as T2/FLAIR and diffusion-weighted imaging. The same technique should be used at baseline and all follow-up scans.

Lesion measurements

Lesions should be measured on T1 weighted postgadolinium images, in the axial plane. The 2 maximal perpendicular outer diameters of each enhancing lesion should be measured. In lesions which have cystic components, areas of necrosis, or surgical cavities, every effort should be made to measure only the solid portions of the lesion, excluding the nonsolid components. In particular, if a patient has a surgical cavity surrounded by enhancement, the cavity should not be included in the measurement. If there is nodular enhancement associated with the cavity, the nodular component alone should be measured.

Baseline tumor documentation

Reviewers will document baseline tumor on postcontrast T1-weighted and T2/FLAIR images. They first identify all lesions, determine whether they are measurable (can be measured), and from these choose target lesions (will be measured throughout the study). To be considered measurable, a lesion has to show enhancement, have 2 perpendicular diameters ≥10 mm, and be suitable for reproducible repeated measurements. Enhancing nonmeasurable lesions include all other enhancement that is strongly believed to represent tumor, but that does not meet the requirements above. Up to 5 lesions can be selected as target. Selected target lesions are measured, and the sum of products of diameters (SPD) calculated. Enhancing nontarget lesions are identified by location only. Because T2/FLAIR abnormalities are typically more diffuse than tumor enhancement, the T2/FLAIR images will be used for comparison when evaluating later visits, without identification of discrete lesions.

Radiographic response assessment

Target lesion response (Table 16) is determined by the change in the sum of diameters from baseline and from nadir (smallest measurement seen until the visit being evaluated):

Table 16 Target Lesion Response

Response	Definition
Complete response	All target lesions have completely disappeared.
Partial response	SPD decreased by ≥50% from baseline value
Stable disease	SPD <50% decreased from baseline, but <25% increased from nadir
Progressive disease	SPD increased by ≥25% from nadir value
Nonevaluable	The sum of diameters cannot be meaningfully evaluated (for example, because of technical factors such as scan quality that obscure one or more target lesions).

Nontarget lesion response (Table 17) is determined by visual inspection of enhancing nontarget lesions collectively and classification into a response category.

Table 17 Lesion Response for Enhancing Nontarget Lesions

Response	Definition
Complete response	All enhancing nontarget lesions have disappeared completely
Stable disease	Enhancing lesions present, showing no definite growth from the visit where they were smallest
Progressive disease	Unequivocal progression of enhancing lesions (see below)
Nonevaluable	The sum of diameters cannot be meaningfully evaluated (for example, because of technical factors such as scan quality that obscure one or more target lesions)

Note on progressive disease: The general approach is that nontarget lesions can be the basis for a determination of progressive disease if it is clear, in the context of the entire scan, that there has been a sufficient increase in the tumor burden to show that treatment has failed.

New lesions are assessed in a binary yes/no fashion. If any new enhancing lesions are present, and the reviewer is confident that these are due to the presence of new malignancy, the response is “Yes,” otherwise, it is “No.” New lesions do not need to meet the size criteria for being considered measurable at baseline, but must, in the best judgment of the reviewer, be true tumor lesions rather than benign or incidental findings, or caused by some comorbidity. If the lesion is uncertain, it should be followed. If later scans reveal it to be a true lesion, the record can be retrospectively updated to show the new lesion at the time it was first identified.

The T2/FLAIR images are reviewed to determine whether there has been an unequivocal increase in tumor-related T2/FLAIR abnormality. This is performed with reference to the scan at which the T2/FLAIR abnormality is smallest (analogous to the nadir measurement for target lesions), and classified as increase, decreased, or unchanged. Because of the frequently diffuse nature of the T2/FLAIR abnormality, it is performed at the scan level rather than by

evaluation of discrete T2/FLAIR lesions. The reviewer must be confident that any recorded increase in T2/FLAIR abnormality is due to tumor rather than some alternative etiology (such as infection, infarction, demyelination, or other causes). If there is question about whether a change seen on T2/FLAIR represents progression, the participant continues to the next scheduled scan. If the subsequent scan confirms progression, the date of progression is assigned retrospectively to the visit where the T2/FLAIR changes were first observed.

Target, nontarget, and new lesions are combined into a radiographic response (Table 18) as follows:

Table 18 Radiographic Response

Target lesions	Enhancing Nontarget lesions	FLAIR/T2 lesions	New lesions	Radiographic Response
CR	CR	No increase	No	CR
CR	SD or NE	No increase	No	PR
PR	CR, SD, or NE	No increase	No	PR
SD	CR, SD, or NE	No increase	No	SD
NED	CR, SD, or NE	No increase	No	NE
PD	Any	Any	Yes/No	PD
Any	PD	Any	Yes/No	PD
Any	Any	Any	Yes	PD
Any	Any	Increased	Yes/No	PD
NA	CR	No increase	No	CR
NA	SD	No increase	No	SD
NA	NA	No increase	No	NED

CR = complete response; FLAIR = fluid-attenuated inversion recovery; NA = no lesions of this type were present at baseline; NED = no evidence of disease (no enhancing lesions were present at baseline, and no new lesions have appeared); PD = progressive disease; PR = partial response; SD = stable disease.

Pseudoprogression associated with radiotherapy

If new or increased enhancement is seen within 12 weeks of the completion of radiation therapy, but the participant is clinically stable and the investigator believes that the changes may be due to pseudoprogression, the participant may remain on treatment. A second scan should be performed, at least 6 weeks after the initial scan. If the enhancement continues to grow on this scan, progression is considered to have been confirmed at the time of the initial scan that showed increased enhancement. If the enhancement has stabilized or decreased on this second scan, the initial scan will be considered to have been confirmed as pseudoprogression. For endpoint assessment purposes, the initial scan will be equivalent to stable disease. On subsequent scans, in cases of confirmed pseudoprogression, all scans before the scan at which pseudoprogression was seen will be excluded when choosing the nadir value against which the size of enhancing lesions is compared.

If the new or increased enhancement occurs in an area that is known to be outside the irradiated area (outside the 80% isodose line), or if the participant shows clinical deterioration not caused by a comorbid condition or changes in steroid dosing, pseudoprogression will not be considered.

Overall Response

To make a final response determination, the radiographic response (from table above) is combined with assessments of clinical status and of corticosteroid dose.

Clinical status is measured using the Karnofsky Performance Scale. A participant's status is considered "stable" if there has been no definite decline in age-adjusted performance from their baseline state, and is considered "worsening" if there has been definite decline in age-adjusted performance that is not attributable to a non-tumor-related cause. Examples of definite decline include a decline from 100 or 90 to 70 or less, a decline of at least 20 points from 80 or less, or a decline from any baseline to 50 or less, unless attributable to comorbid events or changes in corticosteroid dose.

Steroid dose is defined as the average daily dose since last visit. A dose of "none" means no corticosteroids above physiologic replacement dose. The dose is considered "stable" if it is unchanged or decreased from the visit at which the scans showed the smallest tumor burden. The dose is considered "increased" if it has increased from the visit at which the scans showed the smallest tumor burden.

For any overall response except PD, all the components of the definition (radiological, neurological, and steroid dose) must be present (Table 19). However, either radiological progression or clinical deterioration (not attributable to a nontumor-related cause) qualifies a participant for PD. However, an increase in steroid dose alone is not sufficient for an overall visit response of PD in the absence of clinical or radiological evidence of progression. A participant with a radiological response of stable disease, and without neurological evidence of progression, but requiring an increased dose of steroids, would still be considered stable disease overall at that visit (because increase in steroids alone is not PD). However, the participant will be reassessed at the next visit. If either radiological or neurological progression is documented at that next visit, the visit at which the increased dose was first observed would be retroactively reassessed as PD overall.

Table 19 Overall Response

Radiographic Response	Clinical Performance	Steroid Dose	Overall Response
CR	Stable	None	CR
CR	Stable	Stable or increased	PR
PR	Stable	Stable	PR
PR	Stable	Increased	SD
SD	Stable	Stable	SD
SD	Stable	Increased	SD or PD[a]
PD	Any	Any	PD
Any	Worsening	Any	PD
NE	Stable	Increased	NE or PD[a]
NED	Stable	Increased	NED or PD[a]

CR = complete response; NA = no lesions of this type were present at baseline; NED = no evidence of disease (no enhancing lesions were present at baseline, and no new lesions have appeared); PD = progressive disease; PR = partial response; SD = stable disease.

[a] PD should not be based on an increase in steroid dose alone, unless confirmed by radiographic or clinical deterioration. If the steroid dose is increased while the radiographic assessment and clinical performance are stable, the participant should be re-evaluated at the next visit. If clinical or radiographic deterioration has occurred, progression can be retrospectively assigned at the visit when the steroid dose was increased.

Pseudoresponse and response confirmation

Pseudoresponse is a phenomenon observed in patients treated with antiangiogenic therapy, and manifests as a transient decrease in tumor enhancement that does not reflect a true reduction in tumor burden. To avoid mistaken reporting of pseudoresponse as OR, a visit response of PR or CR must be confirmed with a scan performed at least 4 weeks later that shows the same category of response or better. That is, a PR can be confirmed with a subsequent PR or CR, and a CR must be confirmed with a subsequent CR.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
1L	first-line
2L	second-line
ACRIN	American College of Radiology Imaging Network
ADL	activities of daily living
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BP	blood pressure
BRCA	breast cancer susceptibility gene
BTC	biliary tract cancer
BW	body weight
CI	confidence interval
CPK	creatine phosphokinase
CR	complete response
CD28	cluster of differentiation 28
C_{max}	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CVA	cerebrovascular accident
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLTs	dose-limiting toxicities
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
EDC	electronic data collection
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOC	Executive Oversight Committee

Abbreviation	Expanded Term
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-dimension 5-level
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FLAIR	fluid-attenuated inversion recovery
FSH	follicle-stimulating hormone
FU	follow-up
GBM	glioblastoma
gBRCAm	germline breast cancer susceptibility gene mutation
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
iCRO	imaging Contract Research Organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV-type	Ig-variable–type
IHC	immunohistochemistry
IL-10	interleukin 10
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
iRECIST	modified RECIST 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	iRECIST stable disease
IUD	intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MMR	mismatch repair
mRNA	messenger RNA
MRI	magnetic resonance imaging
MSI	microsatellite instability

Abbreviation	Expanded Term
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI	National Cancer Institute
NDA	New Drug Application
NIMP	Non-Investigational Medicinal Product
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PARP	poly (ADP-ribose) polymerase
PBPK	physiologically based PK
PD	progressive disease
PD-1	programmed cell death 1
PDGFR	platelet-derived growth factor receptor
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
q3w	once every 3 weeks
qd	once daily
QoL	quality of life
QLG	Quality of Life Group
QLQ	Quality of life Questionnaire
RANO	Response Assessment in Neuro-Oncology
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome
RTKi	receptor tyrosine kinase inhibitor
RTOG	Radiation Therapy Oncology Group
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIM	site imaging manual
SmPC	Summary of Product Characteristics
SoA	schedule of activities
sSAP	Supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Expanded Term
TAM	tumor-associated macrophage
T1DM	type 1 diabetes mellitus
TAM	tumor-associated macrophage
TGFβ	transforming growth factor, beta 1
T_{lag}	lag time
T_{max}	time to maximum plasma concentration
TMB	tumor mutational burden
TMDD	target-mediated drug disposition
TNBC	triple-negative breast cancer
T-regs	regulatory T-cells
TTD	time to deterioration
UDS	urine drug screen
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
Vp4	portal vein invasion
WOCBP	woman/women of childbearing potential
w/v	weight/volume
ZAP70	zeta-chain-associated protein kinase

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