Official Protocol Title:	A Phase 2, Multicenter, Clinical Study to Evaluate the Safety and Efficacy of MK-1308A (Coformulated MK-1308/MK-3475) in Combination with Lenvatinib (E7080/MK-7902) in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma
NCT Number:	NCT04740307
Document Date:	04-Sep-2024

TITLE PAGE

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Protocol Title: A Phase 2, Multicenter, Clinical Study to Evaluate the Safety and Efficacy of MK-1308A (Coformulated MK-1308/MK-3475) in Combination with Lenvatinib (E7080/MK-7902) in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma

Protocol Number: 004-06

Compound Number: MK-1308A

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

The study is part of a collaboration between MSD and Eisai

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

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Approval Date: 04 September 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 06	04-SEP-2024	To remove unnecessary visits and to adjust other visits to standard of care, since the study has passed the final analysis.
Amendment 05	30-JAN-2024	The protocol was amended to fix an error observed during agency review where some criteria defining a DLT were inadvertently deleted.
Amendment 04	30-OCT-2023	This protocol was amended for study extension. Other minor updates were also made throughout the protocol for clarity and/or additional information.
Amendment 03	02-SEP-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Other minor updates were also made throughout the protocol for clarity and/or additional information.
Amendment 02	02-APR-2021	To clarify the acceptable conditions for the reinitiation of pembrolizumab in the event of MK-1308A discontinuation and to add country-specific protocol requirements.
Amendment 01	22-DEC-2020	To incorporate Health Authority feedback on the DLT criteria and to add the EudraCT number.
Original Protocol	27-OCT-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendments:

To remove unnecessary visits and to adjust other visits to standard of care, since the study has passed the final analysis.

Summary of Changes Table:

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.3, Schedule of Activities	Added a disclaimer above SoA table that study intervention administrations of MK-1308A and pembrolizumab is kept for historical reasons and to be performed per standard of care.	This change was made to update strategy, to remove unnecessary visits and to adjust other visits to standard of care, since the study has passed final analysis. Currently, all participants are on lenvatinib monotherapy, which is standard of care for this patient population.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.3, Schedule of Activities	Inclusion/exclusion: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Participant ID card: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Demographics: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Medical/surgical history: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Allocation: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	MK-1308A or Pembrolizumab Administration: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Tumor Assessment – Chest, Abdomen, and Pelvis (CT/MRI): note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.

Section Number and Name	Description of Change	Brief Rationale
	Child-Pugh Score: Removed scheduled visits and note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Height: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	NYHA: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	ECOG Performance Status: removed scheduled visits and note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	PT/INR: removed scheduled visits and note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	CBC with Differential: removed scheduled visits and note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Clinical Chemistry Laboratory Assessments: removed scheduled visits and note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Urine Dipstick Testing or Urinalysis for Protein: removed scheduled visits and note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	T3/FT3, FT4, and TSH: removed scheduled visits and note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	AFP: removed scheduled visits and note updated to acquire per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	HIV: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Anti-HCV (IgG): removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	If Anti-HCV (IgG) positive: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	HCV genotype: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	HCV viral load: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Anti-HBc (total and IgM)/Anti-HBs/HBV viral load/HBsAg: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.

Section Number and Name	Description of Change	Brief Rationale
	All PK/Pharmacodynamic/Biomarker Assessments: removed heading row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Quavonlimab/Pembrolizumab PK Serum Sample: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Quavonlimab/Pembrolizumab ADA Serum Sample: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Lenvatinib PK Plasma Sample: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Blood for Genetic Analysis: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Blood for Serum Biomarker Analysis: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Blood for RNA Analysis: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Blood for ctDNA Analysis: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Tumor Block or Slides: removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Patient-reported Outcomes: removed heading row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	PROs in the Following Order (EORTC QLQ-C30, EORTC QLQ-HCC18, EQ-5D-5L): removed row.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Footnotes: removed nonapplicable abbreviations.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Footnotes: deleted sentences pertaining to imaging FU from footnote b.	See rationale above for Section 1.3, adjustment of visits to standard of care.
	Footnotes: deleted footnotes (e-h) associated with laboratory / PK / Pharmacodynamic / Biomarker assessments.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 4.1 Overall Design	Added a reference to Appendix 7.	To ensure clarity and adherence to country-specific requirements.
Section 8.1.2 Inclusion/Exclusion criteria	Added disclaimer that the section is kept for historical reasons.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.1.3 Participant Identification Card	Added a disclaimer that the section is kept for historical reasons.	See rationale above for Section 1.3, adjustment of visits to standard of care.

Section Number and Name	Description of Change	Brief Rationale
Section 8.1.4 Medical History	Added a disclaimer that the section is kept for historical reasons.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.1.8 Study Intervention Administration	Added a disclaimer that text pertaining to study intervention administrations of MK-1308A and pembrolizumab is kept for historical reasons and currently, all participants are on lenvatinib monotherapy per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.2, Efficacy/Immunogenicity Assessments	Added a disclaimer that text pertaining to tumor assessments and PROs is kept in this section for historical reasons. PRO is no longer required, and tumor imaging is per standard of care and does not need to be submitted to the BICR vendor.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.3.5 Child-Pugh Score	Added a disclaimer that text pertaining to Child-Pugh score assessments is kept for historical reasons and the assessments are to be performed per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.3.6, Clinical Safety Laboratory Assessments	Added a disclaimer that text pertaining to laboratory tests is kept for historical reasons and testing is to be performed per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.3.8.1 Eastern Cooperative Oncology Group Performance Status	Added a disclaimer that text pertaining to ECOG Performance Status is kept for historical reasons and assessments are to be performed per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.6, Pharmacokinetics	Added a disclaimer that text pertaining to pharmacokinetics is kept for historical reasons and samples for analysis of pharmacokinetics are no longer collected.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.8, Biomarkers	Added a disclaimer that text pertaining to biomarkers is kept for historical reasons and biospecimens for analysis of biomarkers are no longer collected.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 8.10.3.2, Efficacy Follow-up Visits	Added a disclaimer that text pertaining to efficacy follow-up visits is kept for historical reasons and visits should be performed per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 10.2, Appendix 2: Clinical Laboratory Tests	Added a disclaimer that all laboratory assessments are kept for historical reasons and are to be performed per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 10.9, Appendix 9: ECOG Performance Status	Added a disclaimer that text pertaining to ECOG performance status is kept for historical reasons and assessments are to be performed per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.

Section Number and Name	Description of Change	Brief Rationale
Section 10.10, Appendix 10: Child-Pugh Score	Added a disclaimer that text pertaining to Child-Pugh score assessments is kept for historical reasons and assessments are to be performed per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Section 10.12, Appendix 12: NYHA Criteria	Added a disclaimer that text pertaining to NHYA criteria assessments is kept for historical reasons and assessments are to be performed per standard of care.	See rationale above for Section 1.3, adjustment of visits to standard of care.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, Multicenter, Clinical Study to Evaluate the Safety and Efficacy of MK-1308A (Coformulated MK-1308/MK-3475) in Combination with Lenvatinib (E7080/MK-7902) in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma

Short Title: Phase 2 Study of MK-1308A (Coformulated MK-1308/MK-3475), plus Lenvatinib (E7080/MK-7902) in First-line Therapy of Advanced Hepatocellular Carcinoma

Acronym: NA

Hypotheses, Objectives, and Endpoints:

In participants with advanced HCC who have received no prior lines of systemic therapy:

Primary Objective	Primary Endpoint
Objective: To assess the safety and tolerability of study intervention with MK-1308A/lenvatinib.	• Dose-limiting toxicity (DLT) (Safety Lead-in Phase only). • Adverse events (AEs), Serious AEs (SAEs), immune-related AEs (irAEs), and hepatic AEs. • Discontinuing study intervention due to an AE.
Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR). Hypothesis: No hypothesis testing will be performed.	• Objective response (OR): complete response (CR) or partial response (PR).

Secondary Objectives	Secondary Endpoints
Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to duration of response (DOR) per RECIST 1.1 as assessed by BICR.	• DOR: for participants who demonstrate confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to disease control rate (DCR) per RECIST 1.1 as assessed by BICR.	• DCR: BOR of CR, PR, or stable disease (SD) after ≥6 weeks (the start of the window for the first scheduled scan).

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Hepatocellular carcinoma
Population	Participants with advanced hepatocellular carcinoma
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 60 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 110 participants will be allocated.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/Vaccination Regimen	Use
MK-1308A/LENVATINIB	MK-1308A	25 MG QUAVON-LIMAB/ 400 MG PEMBRO-LIZUMAB/ 17.5 ML	25 MG/ 400 MG	IV Infusion	Every 6 weeks	Test Product
MK-1308A/LENVATINIB	Lenvatinib	4 MG	12 MG (BW ≥60 KG) OR 8 MG (BW <60 KG)	Oral	Once Daily	Test Product
MK-1308A/LENVATINIB	PEMBROLIZUMAB (MK-3475)	100 MG / 4 ML	400 MG	IV Infusion	Every 6 weeks	Test Product

BW=body weight; IV=intravenous.

Note: Lenvatinib dosing is based on actual BW at Screening and this weight class will be fixed for the duration of the study. In case of intolerable toxicity to MK-1308A, reinitiation of treatment with pembrolizumab may be considered after discussion with the Sponsor (Section 6.6.1).

Total Number of Intervention Groups/Arms	1 arm
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a Screening phase of up to 28 days, each participant will be assigned to receive study intervention until disease progression is radiographically documented, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment, or until the participant has received up to 2 years of study intervention, whichever occurs first. In the presence of clinical benefit, participants who complete 2 years of treatment may continue to receive lenvatinib alone until progression or intolerable toxicity. After the End-of-Treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, withdrawal of consent, pregnancy, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Steering Committee	No

Study governance considerations are outlined in Appendix 1.

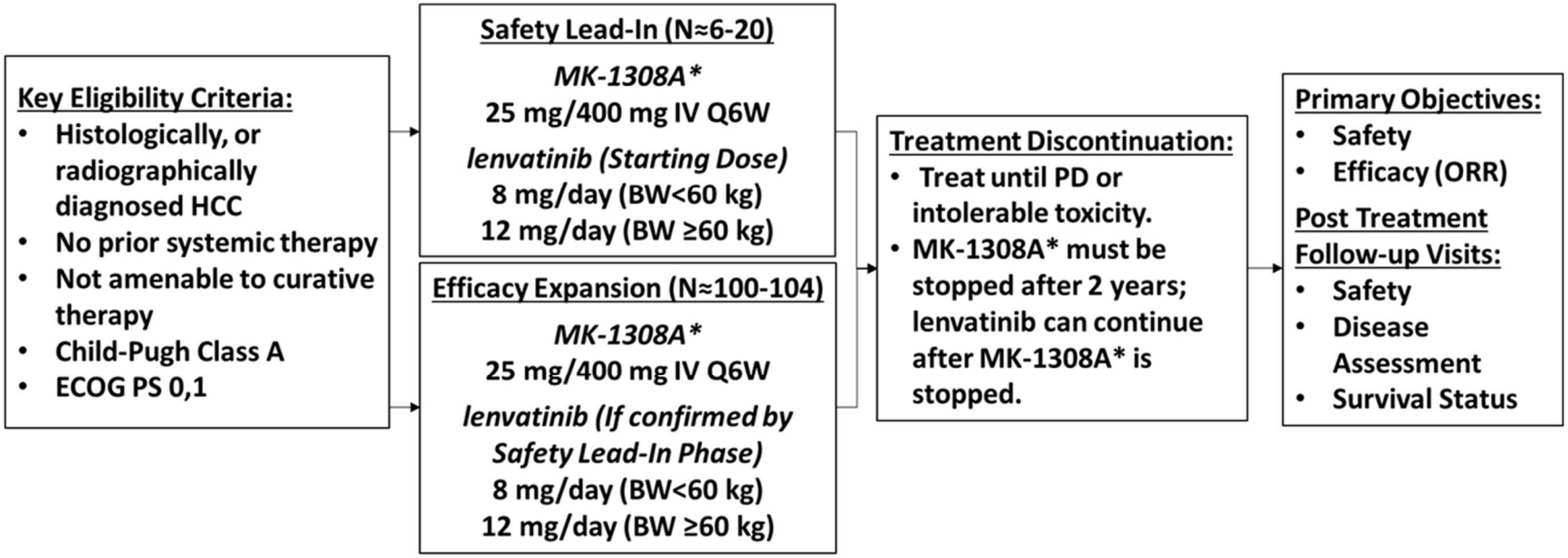
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 14.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram



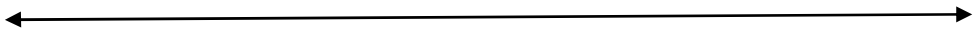
Abbreviations: BW=body weight; HCC=hepatocellular carcinoma; IV=intravenous; PD=progressive disease; ORR=objective response rate; Q6W=every 6 weeks; ECOG PS=Eastern Cooperative Oncology Group Performance Status.

* Note: In case of intolerable toxicity to MK-1308A, reinitiation of treatment with pembrolizumab may be considered after discussion with the Sponsor (Section 6.6.1).

1.3 Schedule of Activities

As of Amendment 6, the Schedule of Activities has been modified to remove study-specific procedures and implement standard-of-care schedules for laboratory assessments and scans.

Table 1 Study Schedule of Activities

	Screening	Treatment Period 21-Day Cycles										EOT	Posttreatment			Notes
Intervention Cycles/ Titles		1			2		3	4	5	6	7 to last					
Cycle Day		1	8	15	1	15	1	1	1	1	1	At D/C	Safety FU[a,b]	Efficacy FU[c]	Survival FU	
Scheduling Window (Days):	–28 to –1		±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	Q9W (±7)	Q12W (±7)	
Administrative and General Procedures																
Informed Consent	X															If the investigator plans to treat beyond disease progression, additional consent is required before continuation of treatment.
Prior/ Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X			Collect concomitant therapy on the same postintervention schedule as AEs and SAEs to capture concomitant meds used to treat AEs/SAEs.
Subsequent Antineoplastic Treatment													X	X	X	All antineoplastic therapy will be recorded until time of death or termination of Survival FU. If a clinic visit is not feasible, follow-up information may be obtained via other means (eg, telephone, video call, mail, or e-mail).
Survival Status																On Sponsor request, participants may be contacted for their survival status at any time during the course of the study.

	Screening	Treatment Period 21-Day Cycles										EOT	Posttreatment			Notes
Intervention Cycles/ Titles		1			2		3	4	5	6	7 to last					
Cycle Day		1	8	15	1	15	1	1	1	1	1	At D/C	Safety FU[a,b]	Efficacy FU[c]	Survival FU	
Scheduling Window (Days):	–28 to –1		±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	Q9W (±7)	Q12W (±7)	
Schedule of Study Intervention																
Lenvatinib Dispensing		X			X		X	X	X	X	X					
Lenvatinib Administration		←	—	—	—	—	—	—	—	—	→					Once daily
Efficacy Procedures																
Tumor Assessment – Chest, Abdomen, and Pelvis (CT/MRI)[c]	X	←	—	—	—	—	—	—	—	—	→	X		X		Tumor assessments to be conducted per standard of care.
Clinical Procedures or Assessments																
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X			Report AEs occurring within 90 days after the last dose of study intervention. Report SAEs occurring within 120 days after the last dose of study intervention.
Full Physical Examination	X												X			To be performed within 7 days before start of study intervention.
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X				C1D8, C1D15, and C2D15 clinic visits are mandatory only during the Safety Lead-in Phase, and can be omitted in Expansion Phase if a home virtual visit is performed.
Child-Pugh Score																Child-Pugh score to be conducted per standard of care.

	Screen-ing	Treatment Period 21-Day Cycles										EOT	Posttreatment			Notes
Intervention Cycles/ Titles		1			2		3	4	5	6	7 to last					
Cycle Day		1	8	15	1	15	1	1	1	1	1	At D/C	Safety FU[a,b]	Efficacy FU[c]	Survival FU	
Scheduling Window (Days):	–28 to –1		±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	Q9W (±7)	Q12W (±7)	
Vital signs (resting BP, pulse, RR, and temp) and weight	X	X	X*	X	X	X	X	X	X	X	X	X	X			C1D8, C1D15, and C2D15 clinic visits are mandatory only during the Safety Lead-in Phase. During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required. * During the Expansion Phase only, if a phone visit is scheduled at C1D8 to report BP and AEs, full vital signs assessment is not required at this visit.
12-Lead ECG	X	X			X					X	X	X	X			ECG at Screening, C1D1, C2D1, D1 of every fourth cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and Safety FU. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants conduct ECG (see Sec. 8.3.3) monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety FU Visits.

	Screen-ing	Treatment Period 21-Day Cycles										EOT	Posttreatment			Notes
Intervention Cycles/ Titles		1			2		3	4	5	6	7 to last					
Cycle Day		1	8	15	1	15	1	1	1	1	1	At D/C	Safety FU[a,b]	Efficacy FU[c]	Survival FU	
Scheduling Window (Days):	–28 to –1		±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	Q9W (±7)	Q12W (±7)	
MUGA or ECHO for LVEF Assessment	X												X			Additional assessments may be performed as clinically indicated. The same assessment method (MUGA or ECHO) should be used throughout the study.
Gastroenterological endoscopy	X															Gastroenterological upper endoscopy at Screening period is necessary only if more than 3 months have passed since the previous assessment.
ECOG Performance Status																Per standard of care.
Local Laboratory Procedures and Assessments[d]																
Pregnancy test (WOCBP only)	X				X		X	X	X	X	X	X	X	X		WOCBP require negative test before allocation. If more than 24 hours have elapsed before first dose of study intervention, another pregnancy test is required before starting study intervention.
PT/INR																Per standard of care.
CBC with Differential																Per standard of care.
Clinical Chemistry Laboratory Assessments																Per standard of care.
Urine Dipstick Testing or Urinalysis for Protein																Per standard of care.

	Screen-ing	Treatment Period 21-Day Cycles										EOT	Posttreatment			Notes
Intervention Cycles/ Titles		1			2		3	4	5	6	7 to last					
Cycle Day		1	8	15	1	15	1	1	1	1	1	At D/C	Safety FU[a,b]	Efficacy FU[c]	Survival FU	
Scheduling Window (Days):	–28 to –1		±3	±3	±3	±3	±3	±3	±3	±3	±3		±7	Q9W (±7)	Q12W (±7)	
T3/FT3, FT4, and TSH																Per standard of care.
AFP																Per standard of care.

Abbreviations: AE=adverse event; AFP=alpha fetoprotein; BP=blood pressure; CBC=complete blood count; CT=computed tomography; D/C=discontinuation; ECG=electrocardiogram; ECHO=echocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT=End-of-Treatment; FT3=free triiodothyronine; FT4=free thyroxine; FU=follow-up; INR=international normalized ratio; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PT=prothrombin time; q6w=every 6 weeks; q9w=every 9 weeks; q12w=every 12 weeks; RR=respiratory rate; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

[a] If EOT visit occurs ≥30 days from last dose of study intervention, a Safety FU visit is not required. In this situation, all procedures required at both the EOT visit and the Safety FU visit should be performed.

[b] Safety FU will occur during 2 separate visits: 30 days AND 90 days after last dose.

[c] After the primary analysis for the study: follow-up visits and tumor assessments should be performed q9w or more frequently if required by local standard of care.

[d] Clinical laboratory assessments may be conducted anytime within 72 hours before the scheduled visit, unless otherwise specified. Procedures/assessments should be performed before administration of study intervention.

Refer to Appendix 7, Section 10.7.2 for country-specific requirements.

2 INTRODUCTION

As of the writing of this protocol, generic names for the components of the MK-1308A coformulation have been devised. For purposes of clarity and readability the combined formulation of "quavonlimab (MK-1308) + pembrolizumab" will be called MK-1308A throughout the document.

2.1 Study Rationale

HCC is one of the leading causes of cancer deaths worldwide. Furthermore, incidence and mortality rates are increasing in most parts of the world, including in the US. Patients with advanced HCC represent a group with high unmet need with low survival rates, few effective therapeutic options, and poor HRQoL [Laube, R., et al 2020].

The combination of immunotherapy and VEGF/VEGFR inhibition has been shown to have superior efficacy in advanced HCC. IMbrave150 showed the superiority of atezolizumab plus bevacizumab versus sorafenib, with OS HR 0.58 (0.42-0.79) and ORR of 27.3% (22.5-32.5) for the combination therapy [Finn, R. S., et al 2020]. Similarly, the combination of pembrolizumab and lenvatinib showed a promising ORR of 36% (26.6–46.2) in the Phase 1b E7080-J081-116/KEYNOTE-524 Study [Finn, R. S., et al 2020a]. No additional toxicity signals were seen for pembrolizumab plus lenvatinib compared with those seen in the individual constituents of this combination, and the benefit:risk profile was favorable. These data show the efficacy of combining IO therapy with VEGF/VEGFR inhibition in advanced HCC.

The CTLA-4 and PD-1 immune checkpoint pathways downregulate T-cell activation which can be exploited by tumors to induce an immunosuppressive state allowing tumors to grow instead of being eliminated by the immune system. CTLA-4 regulates T-cell proliferation early in an immune response, primarily in lymph nodes, whereas PD-1 suppresses T-cells later in an immune response, primarily in peripheral tissues [Buchbinder, E. I. 2016].

The efficacy of CTLA-4 inhibition in advanced HCC has been shown in multiple second-line Phase 2 clinical studies, both as single-agent therapy and in combination with PD-1/PD-L1 inhibitors. In one study, tremelimumab monotherapy had 7.2% (2.4-16.1) ORR, which increased to 24% (14.9-35.3) in combination with durvalumab [Kelley, R. K., et al 2020]. CheckMate-040 showed that the addition of ipilimumab to nivolumab increased ORR to 33% compared with 14% for nivolumab monotherapy [U.S. Prescribing Information 2020]. The data from these Phase 2 studies show the additional efficacy of CTLA-4 inhibition when combined with PD-1/PD-L1 inhibition, with a corresponding but tolerable increase of immune-related toxicity [Kelley, R. K., et al 2020] [Yau, T., et al 2020]. Based on this promising efficacy, a Phase 3 is currently being run evaluating ipilimumab plus nivolumab in 1L HCC (CheckMate 9DW).

The current study will evaluate the fixed dose coformulated product MK-1308A, a humanized anti-CTLA-4 antibody combined with pembrolizumab, plus lenvatinib in a 1L HCC setting. The demonstrated clinical efficacy and acceptable safety profile of pembrolizumab plus lenvatinib in HCC, together with promising anti-CTLA-4 activity as

single-agent and in combination with PD-1/PD-L1 in this disease strongly support further development of MK-1308A plus lenvatinib in participants with 1L advanced HCC.

2.2 Background

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

In recent years, the field of cancer immunotherapy has developed a better understanding of mechanisms by which tumors can limit an immune response. The tumor microenvironment is crucial in mediating escape from immune detection and elimination. In particular, T-cells are kept from achieving activation when cell surface inhibitory receptors are engaged, prohibiting T-cell function. The most notable of these receptors are PD-(L)1 and CTLA-4, both of which have been shown to be viable therapeutic targets in several cancer types through clinical investigation.

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on 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 immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across several indications. For more details on specific indications, refer to the IB.

Clinical studies utilizing anti-CTLA-4 and anti-PD-1 monoclonal antibodies have shown improved efficacy over monotherapy in advanced melanoma. The nivolumab/ipilimumab combination was approved by the FDA as a treatment for patients with unresectable or metastatic melanoma, based on findings from the Phase 3 CheckMate-067 study [U.S. Prescribing Information 2017] [Larkin, J., et al 2015]. This combination has also shown promising efficacy in NSCLC based on data from the Phase 1 CheckMate-012 study, prompting initiation of the Phase 3 CheckMate-227 study. Evidence for combination efficacy in the 2L SCLC population has also been reported from the Phase 1 CheckMate-032 study [Antonia, S. J., et al 2016], prompting the initiation of Phase 3 studies for nivolumab and nivolumab plus ipilimumab as maintenance therapy after 1L chemotherapy (CheckMate 451) and for nivolumab versus chemotherapy as second-line therapy (CheckMate 331) in SCLC. Studies with anti-CTLA-4 and anti-PD-1/PD-L1 are described in Section 2.1.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable

prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; HCC; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

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

2.2.1.2 MK-1308A

MK-1308A is a fixed dose combination of quavonlimab, a humanized anti-CTLA-4 antibody plus pembrolizumab, an anti-PD-1 antibody.

CCI [redacted] This human IgG1 antibody is being developed in combination with pembrolizumab and other therapies to increase antitumor efficacy in patients with CCI [redacted]

CTLA-4 is a negative regulator of T-cell function and proliferation. It is found on the surface of activated T-cells and T-regs as a single-pass transmembrane protein belonging to the immunoglobulin superfamily. CTLA-4 was identified as a second receptor for both CD80 and CD86 and shares some structural homology with the activating coreceptor, CD28. Unlike CD28, which is expressed on naïve T-cells, the cell surface expression of CTLA-4 is both

transient and tightly regulated. The opposing responses mediated by these 2 receptors are capable of coordinating the strength of the immune system's response.

As part of the adaptive immune response, T-cells are central to mounting a defense against tumor growth. Activation of T-cells is achieved via the dual engagement of both the T-cell receptor and CD28 receptor on the T-cell to mount a full immunogenic response. CD28 binds to either CD80 or CD86 molecules expressed on antigen presenting cells, leading to T-cell-specific expression and presentation of CTLA-4, which then competes with CD28 to bind either of these activating molecules, thereby dampening the activation signal for the T-cell, moving it to a more tolerogenic state. Therefore, blocking this immunomodulatory checkpoint, allowing T-cells to remain active, should allow the immune system to mount a more competent and durable antitumor response.

CTLA-4 suppression is thought to act primarily at sites of T-cell activation, eg, secondary lymph organs rather than within the tumor microenvironment. However, inhibition of CTLA-4 results in substantial increases of T-cell infiltrates within tumor tissues. This contrasts with the presumed inhibition of T-cell function via PD-1 engagement which occurs within the tumor microenvironment between T-cells interacting with both antigen presenting cells and the tumor cells themselves. Differences in mechanism and expression of these receptors and their ligands suggest that these differential mechanisms of action may underlie the observed clinical benefit when used as combination therapy above their respective monotherapies.

The humanized antihuman CTLA-4 antibody quavonlimab is being proposed for development in combination with the Sponsor's anti-PD-1 mAb, pembrolizumab (MK-1308A) for use in HCC and CCI [redacted] Two human mAbs targeting CTLA-4, ipilimumab (IgG1) and tremelimumab (IgG2) are in evaluation in the clinic for the treatment of various oncology indications. Ipilimumab is approved for melanoma patients alone and in combination with nivolumab. The combination of ipilimumab and nivolumab has also recently been approved in the United States for the treatment of 2L HCC.

2.2.1.3 Lenvatinib

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 be very important for tumor angiogenesis.

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of HUVEC with IC_{50} values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib showed antitumor activity against various

human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

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

2.2.1.4 Hepatocellular Carcinoma: Epidemiology and Current Therapeutic Options

HCC is responsible for more than 700,000 new cases and 600,000 deaths annually [Dhanasekaran, R., et al 2012]. Most HCC arises in the setting of liver cirrhosis from varied causes, including viral hepatitis, excessive alcohol consumption, and metabolic syndrome. Additionally, HCC incidence varies by region, with the highest rates seen in Eastern Asia and Sub-Saharan Africa (over 20 cases per 100,000 individuals). China accounts for approximately 50% (395,000 new cases annually) of all new HCC cases. Countries in the Mediterranean, including Italy, Spain, and Greece, have intermediate rates, ranging from 10 to 20 cases per 100,000 [Lafaro, K. J., et al 2015], although the incidence in the EU overall (and in Western Europe specifically), as well as in North and South America, is relatively low (<10/100,000) [Ferlay, J., et al 2015].

The predominant risk factors for HCC vary in high- and low-rate regions. In most high-rate countries, particularly Asia and Africa, chronic HBV infection and aflatoxin exposure are the major risk factors [McGlynn, K. A., et al 2015]. In contrast, in lower-rate areas, such as the US, HCV infection, excessive alcohol consumption, and metabolic syndrome play more important roles. Exceptions to these regional patterns are seen in Japan and Egypt, where the predominant risk factor is HCV infection.

Several nonviral risk factors have also been associated with an increased risk for HCC, including alcohol consumption, metabolic syndrome, and hereditary hemochromatosis [Lafaro, K. J., et al 2015] [McGlynn, K. A., et al 2015]. While the increased use of hepatitis B vaccination, combined with effective therapy for hepatitis C will likely lead to a decline of HCC attributed to viral hepatitis, increase in nonalcoholic fatty liver disease, together with metabolic syndrome and obesity, will soon become a leading cause of liver cancer in Western countries [Villanueva, A. 2019].

Surgical resection, transplantation, and ablation are potentially curative treatment options for patients with early-stage HCC; however, about 70% of patients present with advanced, unresectable disease. As HCC is resistant to most traditional chemotherapy agents, the median survival for patients with advanced disease is typically 6 to 9 months without therapy [Qin, S., et al 2013].

Sorafenib, an oral antiangiogenic TKI, is a current standard of care worldwide for the 1L treatment of patients with advanced HCC. In a randomized, open-label, Phase 3 study (REFLECT), lenvatinib (also known as E7080 or MK-7902; hereafter called lenvatinib), an oral multikinase inhibitor, showed noninferiority in terms of OS compared with sorafenib (median OS duration was 13.6 months for lenvatinib vs 12.3 months for sorafenib) [Kudo, M., et al 2018].

Lenvatinib was also approved in Japan, US, EU, and China for first-line treatment of unresectable HCC (see Section 2.2.1.5 for additional information). The combination of atezolizumab/bevacizumab is currently approved in the US and will likely be approved in most of world soon, likely becoming a standard of care for first-line advanced HCC therapy, based on the Phase 3 IMbrave150 study [Finn, R. S., et al 2020].

In addition, multiple other new agents have recently been approved for 2L therapy of HCC, including pembrolizumab, nivolumab and nivolumab+ipilimumab. Regorafenib and cabozantinib are the only globally approved 2L therapies after sorafenib treatment in patients with HCC based on data from Phase 3 studies [Bruix, J., et al 2017] [Abou-Alfa, G. K., et al 2018]. Ramucirumab also reported a positive study for OS versus placebo in a high-risk HCC population with AFP levels ≥400 ng/mL [Zhu, A. X., et al 2018] and is now approved in the US for this patient population. While these agents have shown improved survival, the benefits remain modest, with associated side effects; thus, continued investigation of additional agents for advanced HCC patients remains crucial.

2.2.1.5 Clinical Data on Lenvatinib and Pembrolizumab as Single Agents for the Treatment of HCC

Lenvatinib was approved for first-line treatment of unresectable HCC based on results from the open-label Phase 3 clinical study E7080-G000-304 (REFLECT) study [Kudo, M., et al 2018a]. In data published from the REFLECT study, 954 participants with 1L HCC were randomly assigned to receive lenvatinib at 12 mg or 8 mg qd depending on BW (≥60 kg or <60 kg, respectively [n=478]) or sorafenib at 400 mg twice a day (n=476). Lenvatinib showed noninferior median OS compared with sorafenib (13.6 months vs 12.3 months; HR: 0.92; 95% CI: 0.79–1.06). Lenvatinib treatment also showed improvements when compared with sorafenib treatment in the following: ORR by mRECIST (24.1% vs 9.2%) and PFS (7.4 months vs 3.7 months). The most common any grade AEs for lenvatinib were hypertension (201 [42%]), diarrhea (184 [39%]), decreased appetite (162 [34%]), and decreased weight (147 [31%]). When comparing the AE profile to sorafenib, lenvatinib has a decreased frequency of palmar-plantar erythrodysesthesia (128 [27%] vs 249 [52%]), but an increased frequency of hypertension (201 [42%]) vs 144 [30%]) [Kudo, M., et al 2018a].

Phase 2 data from treatment of 104 participants with pembrolizumab in 2L HCC (KEYNOTE-224) were published [Zhu, A. X., et al 2018a]. These results included an ORR of 17%, with responses seen in HCC of different etiologies, and several participants with prolonged durations of response. Of the 18 responders, 12 (77%) responders showed a response for at least 9 months, as estimated by the Kaplan-Meier method, and the median time to response was 2.1 months (range, 2.1–4.1 months). Treatment-related AEs occurred in 76 (73%) of 104 participants; 16 (15%) were serious. Grade 3 treatment-related events were

reported in 25 (24%) of the 104 participants; the most common were increased AST concentration in 7 (7%), increased ALT concentration in 4 (4%), and fatigue in 4 (4%) of participants. One (1%) Grade 4 treatment-related event of hyperbilirubinemia occurred. One death associated with ulcerative esophagitis was attributed to treatment. Immune-mediated hepatitis occurred in 3 (3%) participants, but there were no reported cases of viral flares. Immune-mediated hepatitis was comparable to that seen in participants treated with pembrolizumab in other indications. KEYNOTE-224 served as the basis for accelerated approval of pembrolizumab in second-line treatment of HCC in the US.

In a Phase 3 study (KEYNOTE-240), 413 participants with advanced HCC were randomized 2:1 to 2L therapy of either pembrolizumab plus BSC or placebo plus BSC. While pembrolizumab did not show statistical superiority over placebo for OS based on the prespecified multiplicity strategy, it was associated with a clinically meaningful improvement in median OS: 13.9 months (95% CI: 11.6, 16.0) for pembrolizumab compared with 10.6 months (95% CI: 8.3, 13.5) for placebo. A treatment effect in OS was apparent in separation of OS curves starting at approximately 3 months. Pembrolizumab also showed a clinically meaningful PFS improvement; the PFS HR was 0.718 (95% CI: 0.570, 0.904; p-value=0.0022) at final analysis, with median PFS of 3.0 months in the pembrolizumab arm versus 2.8 months in the placebo arm, although this also did not meet the prespecified criteria for statistical significance. ORR was consistent with KEYNOTE-224 at 18.3% in the pembrolizumab arm. The safety profile of pembrolizumab, including incidence of immune-mediated events and hepatitis, was similar to that of pembrolizumab in other tumor types. No HBV or HCV viral flares were identified. The most common Grade 3 to 5 treatment-related AEs were increased AST (13.3% vs 7.5%), increased blood bilirubin (7.5% vs 5.2%), ascites (7.2% vs 6.0%), increased ALT (6.1% vs 3.0%), and anemia (3.9% vs 9.0%) in participants treated with pembrolizumab versus placebo, respectively. Grade 3 to 5 immune-mediated AEs were reported in 19 (6.8.%) pembrolizumab-treated participants and 0 (0.0%) participants treated with placebo, the most common of which were hypothyroidism, hyperthyroidism, pneumonitis, and colitis. The magnitude of benefit as captured by the HR for OS and PFS, the ORR and response duration are consistent with the findings of KEYNOTE-224. Taken together, these data support that the benefit:risk balance for pembrolizumab is favorable in the second-line setting for advanced HCC.

2.2.1.6 Clinical Data on Lenvatinib in Combination With Pembrolizumab for Treatment of HCC

The combination of pembrolizumab plus lenvatinib shows promise in multiple other tumor types (renal cell carcinoma, endometrial cancer, squamous cell carcinoma of the head and neck, melanoma, NSCLC, or urothelial cancer [Taylor, M. H., et al 2020], and advanced endometrial carcinoma [Makker, V., et al 2020]). See Section 4.3 – Justification for Dose for additional information.

A Phase 1b/2 study of the combination of lenvatinib and pembrolizumab in HCC (Study E7080-J081-116/ MK-3475-524) using weight-based dosing showed promising data [Finn, R. S., et al 2020a]. No DLTs were reported in Part 1 [Llovet, J. M., et al 2019]. The MTD was determined as 12 mg (≥60 kg BW) or 8 mg (<60 kg BW) lenvatinib orally qd in combination with 200 mg IV q3w of pembrolizumab. As of data cutoff, 31-OCT-2019, 104

participants were enrolled (Part 1, n=6; Part 2, n=98), with 100 participants having no prior systemic therapy. There was a manageable safety profile for the combination and notable antitumor activity. The most common any grade treatment-related AEs were hypertension (36%), diarrhea (35%), fatigue (30%), decreased appetite (28%), and hypothyroidism (25%). The most common Grade 3 treatment-related AE was hypertension (17%) [Finn, R. S., et al 2020a]. The ORR, excluding unconfirmed responses, for the 100 first-line participants was 36% (95% CI: 26.6%–46.2%) by RECIST 1.1 and 46% (95% CI: 36% – 56.3%) by mRECIST as assessed by BICR. The PFS was 8.6 months (95% CI: 7.1 – 9.7) by RECIST 1.1 and 9.3 months (95% CI: 5.6–9.7) by mRECIST, with a median OS of 22 months (95% CI: 20.4-NE).

LEAP-002 is an ongoing Phase 3 study evaluating pembrolizumab/lenvatinib vs placebo/lenvatinib in advanced HCC. This study may serve to establish pembrolizumab/lenvatinib combination as standard of care for this patient population.

2.2.2 Preclinical and Clinical Studies

Refer to the respective IBs for preclinical and clinical study data for quavonlimab /MK-1308A and lenvatinib.

2.2.3 Ongoing Clinical Studies

Refer to the respective IBs for ongoing clinical study data for quavonlimab /MK-1308A and lenvatinib.

2.3 Benefit/Risk Assessment

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

As discussed in Sections 2.2.1.1 and 2.2.1.3, both pembrolizumab and lenvatinib (alone and in combination), have shown promising efficacy in participants with HCC, and preliminary safety data of the combination of lenvatinib and pembrolizumab suggest toxicity is manageable. Although quavonlimab has not been studied in HCC patients, anti-CTLA-4 therapy has been shown to have efficacy in this disease, and a combination of an anti-PD-1 and anti-CTLA-4 therapy has received accelerated approval in the US. Therefore, given the limited treatment options for patients with advanced HCC, there is an unmet medical need for novel therapies in this setting. The existing data suggest that inhibiting angiogenesis in combination with PD-1 and CTLA-4 blockade is a promising therapeutic strategy, and the benefit:risk assessment for participants included in this study is considered to be favorable. No unexpected risks have been reported in HCC with other immune check point inhibitors other than transient elevations in ALT and AST.

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 advanced HCC who have received no prior lines of systemic therapy:

Primary Objective	**Primary Endpoint**
Objective: To assess the safety and tolerability of study intervention with MK-1308A/lenvatinib.	• Dose-limiting toxicity (DLT) (Safety Lead-in Phase only). • Adverse events (AEs), Serious AEs (SAEs), immune-related AEs (irAEs), and hepatic AEs. • Discontinuing study intervention due to an AE.
Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR). Hypothesis: No hypothesis testing will be performed.	• Objective response (OR): complete response (CR) or partial response (PR).
Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to duration of response (DOR) per RECIST 1.1 as assessed by BICR.	• DOR: for participants who demonstrate confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to disease control rate (DCR) per RECIST 1.1 as assessed by BICR.	• DCR: BOR of CR, PR, or stable disease (SD) after ≥6 weeks (the start of the window for the first scheduled scan).
Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to progression-free survival (PFS) per RECIST 1.1 as assessed by BICR.	• PFS: the time from the first dose of study intervention to the first documented disease progression or death due to any cause, whichever occurs first.

Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to time to progression (TTP) per RECIST 1.1 as assessed by BICR.	• TTP: time from the first dose of study intervention to the first documented disease progression.
Objective: To evaluate the efficacy of MK-1308A/lenvatinib with respect to overall survival (OS).	• OS: the time from the first dose of study intervention to death due to any cause.
Objective: To evaluate efficacy outcomes of MK-1308A/lenvatinib per mRECIST assessed by BICR.	• ORR, DOR, DCR, PFS, and TTP.
CCI [redacted]	CCI [redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, single-arm study of MK-1308A/lenvatinib in first-line intervention in participants with advanced HCC. This study protocol will have 2 phases: an initial Safety Lead-in Phase, in which the preliminary RP2D of MK-1308A/lenvatinib will be established, followed by an Efficacy Expansion Phase.

Approximately 6-20 participants will be allocated in the Safety Lead-in Phase, depending on DLTs; note that if no DLTs are observed in the first 6 participants, the Safety Lead-in Phase could be complete. Subsequently, approximately 100-104 participants will be allocated in the Efficacy Expansion Phase, for a total of approximately 110 participants on Dose Level 0. Participants will receive MK-1308A 25 mg/400 mg IV q6w plus lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally qd.

Lenvatinib dosing is based on actual BW at Screening and this weight class will be fixed for the duration of the study. MK-1308A will be administered for up to 2 years. Lenvatinib will be administered until PD or unacceptable toxicity.

Discontinuation of MK-1308A may be considered for participants who have attained a confirmed CR and have been treated with at least 4 doses (approximately 24 weeks), receiving at least 1 dose of MK-1308A beyond the date when the initial CR was declared.

The primary objectives of this study are to assess the safety and ORR per RECIST 1.1 by BICR in participants treated with MK-1308A/lenvatinib. Only participants who start at Dose Level 0 (MK-1308A 25 mg/400 mg IV q6w plus lenvatinib 12 mg [BW ≥60 kg] or 8 mg [BW <60 kg] orally qd) will be evaluable for primary objective ORR. On study imaging assessments will be performed q9w calculated from the date of first dose and independent of treatment delays. RECIST 1.1 will be used by the site for treatment decisions until the first radiologic evidence of PD. Participants who experience disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted by telephone or visit approximately q12w, or more frequently to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Interim analyses in the protocol are described in Section 9.7 - Interim Analyses.

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

For country-specific requirements see Appendix 7.

4.1.1 Safety Lead-in Phase

The RP2D for lenvatinib, lenvatinib/pembrolizumab, and quavonlimab/pembrolizumab were established in separate, prior Phase 1 studies and will be considered for determining the starting dose for the Safety Lead-in Phase in this study. The Safety Lead-in Phase will use an

mTPI design [Ji, Y. and Wang, S.-J. 2013] with a target DLT rate of 35%, to identify the RP2D of lenvatinib in combination with MK-1308A. An event will be considered a DLT if it occurs during the prespecified time period of 1 cycle (3 weeks) from the first dose of study intervention and meets at least 1 of the criteria described in Section 6.6.3.

There are 2 predetermined dose levels of MK-1308A and lenvatinib that may be explored (Dose Level 0 and Dose Level -1, Table 2) in the mTPI design.

Table 2 Predetermined Dose Levels for MK-1308A and Lenvatinib

	Dose Level 0	**Dose Level -1**
MK-1308A	25 mg / 400 mg	25 mg / 400 mg
Lenvatinib	12 mg (BW ≥60 kg) 8 mg (BW <60 kg)	8 mg (BW ≥60 kg) 4 mg (BW <60 kg)

Initially, 3 participants will be allocated to Dose Level 0. More than 3 participants may be allocated to Dose Level 0 if needed to replace participants who are not evaluable for DLT as per Section 5.5. The initial 3 participants will be evaluated for DLTs for 1 cycle (3 weeks) from first dose of study intervention before further allocation. For the first 3 participants, there is also a mandatory 24-hour pause between participants; the 24-hour pause between participants begins at the time that the dose of study intervention is administered.

The criteria for DLTs are described in Section 6.6.3. Participants who experience a DLT will be allowed to remain on the study if they meet the following criteria: (1) the investigator believes it is appropriate for participant to remain on the study, and (2) the event has resolved and no longer meets the definition of DLT. Dose recommendations for the next participants enrolled will depend on the observed number of DLTs in the first 3 DLT-evaluable participants and the mTPI table (Table 3). The actions in the table are designed to ensure that if the initial dose level is too toxic, newly allocated participants will be treated at a lower dose level. If the dose is deescalated, a 24-hour pause between the first 3 participants at the new dose level will also be used. The Safety Lead-in Phase ends when approximately 10 participants that qualify for DLT evaluation are allocated and treated at 1 of the 2 doses in Table 2. There is also a possibility to end the Safety Lead-in Phase when at least 6 DLT-evaluable participants have been treated at Dose Level 0 with 0 observed DLTs (see Section 4.3.2.1 for details).

4.1.2 Efficacy Expansion Phase

Allocation will be opened for the Efficacy Expansion Phase only if Dose Level 0 is determined to be tolerable. In this case, 100-104 participants will be enrolled at Dose Level 0 in the Efficacy Expansion Phase, depending on how many participants were enrolled in the Safety Lead-in Phase (110 minus the number of participants in the Safety Lead-in Phase).

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The study includes the primary efficacy endpoint of ORR per RECIST 1.1 as assessed by BICR.

ORR 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 benefit:risk profile. Images will be read per RECIST 1.1 by BICR to minimize bias in the response assessments.

The secondary efficacy objectives of this study are to evaluate: 1) DOR per RECIST 1.1 assessed by BICR, 2) DCR per RECIST 1.1 assessed by BICR, 3) PFS per RECIST 1.1 assessed by BICR, 4) TTP per RECIST 1.1 assessed by BICR, 5) OS, and 6) ORR, DOR, DCR, PFS, and TTP per mRECIST assessed by BICR.

Exploratory efficacy objectives of this study include evaluating ORR, DOR, DCR, PFS, and TTP per 1) RECIST 1.1 assessed by investigator, and 2) iRECIST assessed by investigator.

DCR and DOR per RECIST 1.1 assessed by BICR will serve as additional measures of efficacy and are commonly accepted endpoints by both regulatory authorities and the oncology community.

PFS 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 benefit:risk profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by an iCRO blinded to treatment assignment to minimize bias in the response assessments.

The endpoint of OS is the standard for demonstrating superiority of antineoplastic therapy in clinical studies for HCC.

Measurable disease will be confirmed centrally 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.

4.2.1.1.1 Response Rate Assessed by RECIST Version 1.1

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

4.2.1.1.2 Response Rate Assessed by Modified Response Evaluation Criteria in Solid Tumors 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 pembrolizumab (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 provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor 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 10% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

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

4.2.1.1.3 Modified RECIST

Modified RECIST for HCC allows evaluation of treatment effects that are not reflected in simple total size changes of lesions. Specifically, mRECIST allows assessment of treatment-related tumor necrosis and assessment of viable tumor by assessment with arterial phase imaging. Details are fully described in [Lencioni, R. 2010], and key differences from RECIST 1.1 are listed in Section 8.2.1.6.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, v5.0.

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the benefit:risk profile of any new study intervention. As part of the analyses for this study, HRQoL and disease-related symptoms will be investigated among all participants via the following assessment tools: EORTC QLQ-C30, EORTC QLQ-HCC18, and the EuroQoL EQ-5D-5L questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30

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

4.2.1.3.2 EORTC QLQ-HCC18

The EORTC QLQ-HCC18 is a disease-specific questionnaire developed and validated to address measurements specific to HCC [Blazeby, J. M., et al 2004]. 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 18 items containing 6 scales and 2 single items.

4.2.1.3.3 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, 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 participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.4 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 MK-1308A to support the proposed dosing regimen.

4.2.1.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

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4.3 Justification for Dose

4.3.1 MK-1308A

MK-1308A is coformulated at a fixed dose of 25 mg MK-1308 (quavonlimab) plus 400 mg MK-3475 (pembrolizumab) to be administered q6w. The formulation and dosing regimen were chosen after safety and efficacy analyses were performed on 215 participants from MK-1308-001 with advanced malignancies treated with quavonlimab plus pembrolizumab at various doses and schedules (see IB for further details).

In summary, evaluation of the safety, tolerability, PK, pharmacodynamics, and efficacy analysis of that study showed that CCI

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The current approved dosing regimens of pembrolizumab for IV administration are 200 mg q3w and 400 mg q6w for adults.

A 400 mg q6w dosing regimen of pembrolizumab is expected to have a similar benefit:risk profile as 200 mg q3w, in all treatment settings in which 200 mg q3w pembrolizumab is currently approved [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg q6w for pembrolizumab is considered adequate based on modeling and simulation analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures:
  - Average concentration (C_{avg}) over the dosing interval or AUC at 400 mg q6w is similar to that at the approved 200 mg q3w dose, thus bridging efficacy between dosing regimens.
  - Trough concentrations (C_{min}) at 400 mg q6w are generally within the range of those achieved with 2 mg/kg or 200 mg q3w in the majority (>99%) of participants.
  - Peak concentrations (C_{max}) at 400 mg q6w is well below the C_{max} for the highest clinically tested dose of 10 mg/kg q2w, supporting that the safety profile for 400 mg q6w should be comparable to the established safety profile of pembrolizumab.
  - Exposure-response for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg q6w is expected to be similar to that at 200 mg or 2 mg/kg q3w, given the similar exposures; thus 400 mg q6w is expected to be efficacious across indications.

The rationale for coformulation proposed to be evaluated in this study is to CCI
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4.3.2 Lenvatinib

The starting dose of lenvatinib for this combination study will be 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally qd. Based on dose modification results in an earlier Phase 1/2 study of lenvatinib in participants with HCC (E7080-J081-202) and population PK analyses showing higher lenvatinib AUC and lower BW resulting in earlier drug withdrawal or dose reduction, 2 different starting doses were planned in a Phase 3 study of lenvatinib monotherapy in participants with unresectable HCC (E7080-G000-304): 12 mg for participants with BW ≥60 kg and 8 mg for participants weighing <60 kg. The final PK model including data from E7080-G000-304 confirmed that lenvatinib was affected by BW. The decrease in CL/F in participants with low BW resulted in an increase in lenvatinib AUC. The median value and range of individual AUCs at steady state for participants in E7080-G000-304 were comparable between the 8 mg starting dose group for BW <60 kg and the 12-mg dose group for BW ≥60 kg. Furthermore, a similar median OS was observed in both BW subgroups (BW ≥60 kg and <60 kg: 13.7 months and 13.4 months, respectively),

and the HR favored lenvatinib in both subgroups (HR: 0.95 and 0.85, respectively). Lastly, the duration-adjusted rate of TEAEs was similar for participants treated with either starting dose. These findings support the appropriateness of the lower starting dose of 8 mg for participants with BW <60 kg.

4.3.2.1 Modified Toxicity Probability Interval in the Safety Lead-In Phase

Dose-finding in the Safety Lead-in Phase will use an mTPI design [Ji, Y., et al 2007] with a target DLT rate of 35% (inclusive) to identify the RP2D of lenvatinib in combination with MK-1308A. An event will be considered a DLT if it occurs during the prespecified time period of 1 cycle (as defined in Section 4.1.1) from the first dose of study intervention and meets at least 1 of the criteria described in Section 6.6.3.

Initially, 3 participants will be allocated to Dose Level 0. The initial 3 participants will be evaluated for DLTs for 1 cycle (3 weeks) from first dose of study intervention before further allocation. Dose recommendations for the next participants enrolled will depend on the observed number of DLTs in the first 3 DLT-evaluable participants and the mTPI table (Table 3). In Table 3, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing a DLT. The entries of the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, deescalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. For example, if 0 of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. Dose would not be escalated above Dose Level 0, so an “Escalate” can also mean “Stay”. If 2 of 3 participants develop a DLT, the dose will be deescalated to Dose Level -1. If 3 of 3 participants develop a DLT, this indicates an unacceptable toxicity at Dose Level 0, and the study dose will be paused by the Sponsor to evaluate treatment options. If 1 of 3 participants at a given dose level develops a DLT, then additional participants should be allocated at that dose level following the rules below.

When adding participants to a dose level in response to a “Stay” decision, the number of additional participants to be allocated is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 3). Second, to determine how many more participants can be allocated at the dose level, count steps in diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants have experienced a DLT at a given dose level, no more than an additional 4 participants should be allocated at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 4 of the additional participants experience a DLT (ie, 5 of 7 participants with a DLT in Table 3).

A decision of D or DU at Dose Level -1 will stop the evaluation of the combination under study. An E decision at Dose Level 0 will result in staying at that level. During dose finding, it may be acceptable to deescalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 new participants may be allocated at the new intermediate dose, and the aforementioned rules should be used to determine further allocation at this dose level.

After 10 DLT-evaluable participants have been allocated at any of the tested doses (including intermediate doses), dose finding will stop if the mTPI table indicates S for staying (or E in the absence of higher dose levels). Dose finding may also stop if 6 DLT-evaluable participants have been allocated at Dose Level 0 with 0 observed DLTs among those 6 participants (as even 4 DLTs in an additional 4 participants would still result in a "stay" decision at this dose). Allocation will be opened for the Efficacy Expansion Phase only if Dose Level 0 is determined to be tolerable. Allocation in the Efficacy Expansion Phase may also open before all 10 participants completing the DLT period if enough participants have completed the DLT period and further information from those that have not yet completed the DLT evaluation would not be enough to change the dose decision as per mTPI guidelines in Table 3.

The pool-adjacent-violators algorithm [Ji, Y., et al 2007] may be used to estimate the DLT rates across doses. The dose with an estimated DLT rate up to 35% will be treated as a preliminary MTD. However, the totality of the data will be considered before deciding whether Dose Level 0 will be carried forward to the Efficacy Expansion Phase. The escalation schedule may be adjusted based on safety data emerging throughout the study.

Note that although 35% (inclusive) was the target toxicity rate used to generate the guidelines in Table 3, the observed rates of participants with DLTs at the MTD may be slightly above or below 35%.

Table 3 Dose Finding Rules per mTPI Design

	Number of Participants Evaluable for DLT at Current Dose							
Number of participants with at least 1 DLT	3	4	5	6	7	8	9	10
0	E	E	E	E	E	E	E	E
1	S	S	E	E	E	E	E	E
2	D	S	S	S	S	S	S	E
3	DU	D	D	S	S	S	S	S
4		DU	DU	D	D	S	S	S
5			DU	DU	DU	D	D	S
6				DU	DU	DU	DU	D
7					DU	DU	DU	DU
8						DU	DU	DU
9							DU	DU
10								DU

D=Deescalate to the next lower dose; DLT=dose-limiting toxicity; DU=The current dose is unacceptably toxic; E=Escalate to the next higher dose; mTPI=modified Toxicity Probability Interval; S=Stay at the current dose.

Note: Target toxicity rate = up to 35% (inclusive). Flat noninformative prior Beta (1,1) is used as a prior and $\varepsilon1=\varepsilon2=0.05$ [Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013] [Ji, Y., et al 2010]

4.3.3 Maximum Dose/Exposure for This Study

The maximum dose/exposure of MK-1308A allowed in this study is 25 mg/400 mg q6w up to 2 years. The maximum dose for lenvatinib is 12 mg/day; lenvatinib will be continued 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 contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

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

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

Participants with HCC will be allocated in this study.

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has an HCC diagnosis confirmed by radiology, histology, or cytology (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible).

- Radiologic confirmation of diagnosis is provided by the study site and confirmed by BICR. Clinically confirmed diagnosis of HCC as per the AASLD criteria (Appendix 13), which requires:
    - Radiographically evident cirrhosis AND
    - A liver mass that shows arterial phase hyperenhancement on triphasic CT or MRI, AND EITHER:
        - Is ≥20 mm with either nonperipheral portal washout or an enhancing capsule

          OR
        - Is 10-19 mm with nonperipheral portal venous washout AND an enhancing capsule

2. Has BCLC Stage C disease, or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach (see Appendix 11).
3. Has a Child-Pugh class A liver score within 7 days before first dose of study intervention (see Appendix 10).
4. Has a predicted life expectancy of >3 months.
5. Has at least 1 measurable HCC lesion based on RECIST 1.1, confirmed by BICR.

Demographics

6. Has an ECOG PS of 0 to 1 within 7 days before first dose of study intervention.

7. Is an individual of any sex/gender, is at least 18 years, at the time of providing the informed consent.

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 receiving 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 are more stringent than the requirements above, the local label requirements should 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 one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after MK-1308A and 30 days after lenvatinib, whichever occurs last after the last dose of study intervention. The investigator should evaluate the potential for contraceptive

method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

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

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

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.

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

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

Informed Consent

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

Additional Categories

11. Participants with past or ongoing HCV infection will be eligible for the study. The treated participants must have completed their treatment at least 1 month before starting study intervention.

12. Participants with controlled hepatitis B will be eligible as long as they meet the following criteria:

- Antiviral therapy for HBV must be given for at least 4 weeks and HBV viral load must be less than 500 IU/mL before first dose of study intervention. Participants on active HBV therapy with viral loads under 500 IU/mL should stay on the same therapy throughout study intervention.

- Participants who are positive for antihepatitis B core antibody HBc, negative for HBsAg, and negative or positive for antihepatitis B surface antibody (HBs), and who have an HBV viral load under 100 IU/mL, do not require HBV antiviral prophylaxis.

13. Has adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg at Screening and no change in antihypertensive medications within 1 week before Cycle 1 Day 1.

14. Has adequate organ function as defined in Table 4. Specimens must be collected within 7 days before the start of study intervention.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥75,000/µL
Hemoglobin	≥8 g/dL without transfusion or EPO dependency[a]
Renal	
Creatinine OR Measured or calculated creatinine clearance (CrCl)[b] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥40 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤2 mg/dL OR direct bilirubin ≤ULN for participants with total bilirubin levels >2 mg/dL
AST (SGOT) and ALT (SGPT)	≤5 × ULN
Amylase and lipase	≤1.5 × ULN
Albumin[c]	>3.0 g/dL
Coagulation	
INR OR PT	≤2 OR ≤1.5xULN

ALT (SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); ANC=absolute neutrophil count; AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); EPO=erythropoietin; GFR=glomerular filtration rate; INR-international normalized ratio; PT=prothrombin time; ULN=upper limit of normal.

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

[b] Creatinine clearance should be calculated per institutional standard.

[c] No albumin supplement allowed within the last 14 days.

Note: This table includes eligibility-defining laboratory value requirements for treatment.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has had esophageal or gastric variceal bleeding within the last 6 months. All participants will be screened for esophageal or gastric varices unless such screening has been performed in the past 3 months before first dose of treatment. If varices are present, they should be treated according to institutional standards before starting study intervention; esophageal or gastric varices that require interventional treatment within 28 days before first dose of study intervention are excluded.

2. Has bleeding or thrombotic disorders or use of factor X inhibitors or anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin is permitted.

3. Has clinically apparent ascites on physical examination.

   Note: ascites that resolve to clinically undetectable with medication or are detectable on imaging studies only are allowed.

4. Has inferior vena cava or cardiac involvement of HCC based on imaging, confirmed by BICR.

5. Has had clinically diagnosed hepatic encephalopathy in the last 6 months unresponsive to therapy. Participants on rifaximin or lactulose during Screening to control their hepatic encephalopathy are not allowed.

6. Has medical contraindications that preclude all forms of contrast-enhanced imaging (CT or MRI).

7. Has gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.

8. Has a preexisting Grade ≥3 gastrointestinal or nongastrointestinal fistula.

9. Has active hemoptysis (bright red blood of a least 0.5 teaspoon) within 3 weeks before the first dose of study intervention.

10. Has clinically significant cardiovascular impairment within 12 months of the first dose of study intervention, including NYHA Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability (see Appendix 12). Note: Medically controlled arrhythmia would be permitted.

11. Has had major surgery to the liver within 4 weeks before the first dose of study intervention.

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

12. Has had a minor surgery (ie, simple excision) within 7 days before the first dose of study intervention (Cycle 1 Day 1).

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

Prior/Concomitant Therapy

14. Has received any systemic chemotherapy, including anti-VEGF therapy, or any systemic investigational anticancer agents for treatment of HCC.

    Note: Participants who have received local hepatic chemotherapy are eligible.

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

16. Has received locoregional therapy to liver (transcatheter chemoembolization, transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation) within 4 weeks before the first dose of study intervention.

    Note: Participant must show evidence of disease progression after locoregional therapy to be eligible.

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

18. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Note: Killed vaccines are allowed. Refer to Section 6.5.2 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

19. Is currently participating in or has participated 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 since the last dose of the previous investigational agent.

Diagnostic Assessments

20. 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.

21. Known additional malignancy that is progressing or has required active treatment within the past 3 years.

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

22. Has a known history of, or any evidence of, CNS metastases and/or carcinomatous meningitis as assessed by local site investigator.

23. Has severe hypersensitivity (≥Grade 3) to study intervention and/or any of their excipients.

24. Has an active autoimmune disease that has required systemic treatment in the 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.

25. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

26. Has urine protein ≥1 g/24 hours. Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria.

27. Has prolongation of QTcF interval to >480 ms.
    NOTE: If the QTcF is prolonged to >480 ms in the presence of a pacemaker, contact the Sponsor to determine eligibility.

28. Has LVEF below the institutional normal range as determined by MUGA or ECHO.

29. Has an active infection requiring systemic therapy with the exception of HBV or HCV.

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

31. Has dual active HBV infection (HBsAg (+) and/or detectable HBV DNA) and HCV infection (anti-HCV Ab (+) and detectable HCV RNA) at study entry.

32. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it 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 the participant’s ability to cooperate with the requirements of the study.

Other Exclusions

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

5.3 Lifestyle Considerations

No additional restrictions are required.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

To determine safety in the Safety Lead-in Phase, all participants selected must meet the criteria for evaluability in the first 3 weeks of study intervention (DLT window). Participants are considered nonevaluable for DLT assessment and will be replaced if:

- They are allocated but not treated.
- They discontinue from the study before completing all the safety evaluations during the DLT window for reasons other than treatment-related AEs (eg, disease progression).
- They discontinue from the study treatment before completing the DLT window and do not experience a DLT before discontinuation.
- They receive <75% of the total investigational agent infusion (eg, because the infusion has to be discontinued due to an infusion reaction) and do not experience a DLT.

DLT nonevaluable participants will not be included in the DLT evaluation in the Safety Lead-in Phase.

If a participant experiences a DLT in the Safety Lead-in Phase, the investigator and Sponsor will discuss the case. If the investigator feels the participant is deriving clinical benefit from the study intervention and is deemed clinically stable, the participant may be allowed to continue if agreed to by the Sponsor. Otherwise, the participant should discontinue study intervention. Participants must meet the following criteria for clinical stability:

- Participants must have adequate organ function as indicated by the laboratory values;
- Participants must have no evidence of disease progression; and
- Participants must have an ECOG performance status of 0 or 1.

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 of MK-1308A, pembrolizumab, and lenvatinib will be packaged to support enrollment as required. 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 5.

Country-specific requirements are noted in Appendix 7.

Table 5 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
MK-1308A/ LENVATINIB	Experimental	MK-1308A	Drug	Solution	25 MG QUAVON-LIMAB/ 400 MG PEMBRO-LIZUMAB / 17.5 ML	25 MG/ 400 MG	IV Infusion	Every 6 weeks	Test Product	IMP	Centrally by Sponsor
MK-1308A/ LENVATINIB	Experimental	Lenvatinib	Drug	Capsule	4 MG	12 MG (BW ≥60 KG) OR 8 MG (BW <60 KG)	Oral	Once Daily	Test Product	IMP	Centrally by Sponsor
MK-1308A/ LENVATINIB	Experimental	PEMBROLIZUMAB (MK-3475)	Drug	Solution	100 MG / 4 ML	400 MG	IV Infusion	Every 6 weeks	Test Product	IMP	Centrally by Sponsor

BW=body weight; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product. 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.

Note: Lenvatinib dosing is based on actual BW at Screening and this weight class will be fixed for the duration of the study.

If toxicities resolve and conditions as per are met, MK-1308A may be restarted at the discretion of the investigator. Alternatively, reinitiation of treatment with pembrolizumab may be considered after discussion with the Sponsor (Section 6.6.1).

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

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-1308A, pembrolizumab, and lenvatinib 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 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

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation 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 MK-1308A and for other allowed dose interruptions of MK-1308A.

Resuming lenvatinib dosing after an interruption >28 consecutive days and restarting MK-1308A or pembrolizumab after an interruption >12 weeks requires communication between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

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

All concomitant medications received within 28 days before the first dose of study intervention and up to 90 days after the last dose of study intervention should be recorded. Concomitant medications administered 120 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.7.

6.5.1 Allowed Concomitant Medication

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Palliative radiotherapy is permitted to a single lesion on an exceptional case-by-case basis after communication with the Sponsor if considered medically necessary by the treating physician, as long as the lesion is NOT a RECIST 1.1-defined target lesion and radiotherapy is NOT administered for tumor control. MK-1308A 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 can be continued per investigator discretion during the palliative radiation. The specifics of the radiation treatment, including the location, will be recorded on the CRF.

6.5.2 Prohibited Concomitant Medications

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), antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy not specified in this protocol
- Investigational agents other than MK-1308A, pembrolizumab, or lenvatinib
- Locoregional therapy
- Radiation therapy
  Note: Radiation for pain or palliation is acceptable (see Section 6.5.1).
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.
  Note: Killed vaccines are allowed.

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

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after communication with the Sponsor. Exception: steroids may be used for premedication before imaging.

Anticoagulants that require INR monitoring, such as warfarin (treatments that do not require INR monitoring, such as low molecular weight heparin, are permitted) are prohibited in combination with lenvatinib therapy.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments should consult with Sponsor before resuming study intervention.

It is important for investigators to review each medication (prescription and nonprescription) the participant is taking before starting the study and at each study visit.

- At each visit, participants should be questioned about any new drug they are taking.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are absolutely essential.
- Drugs known to be hepatotoxic (ie, drugs with a warning of hepatotoxicity in the package insert) should be avoided during the dosing period. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nih.gov website.

The following medications/therapies should be avoided during the dosing period and for 14 days thereafter:

<u>Herbal Supplements/Alternative Medicines</u>

- Anticancer herbal supplements or alternative medicines (including approved traditional Chinese medicines for HCC) are strongly discouraged during the Screening and Treatment Phase of this study.

The exclusion criteria describe other medications that are prohibited in this study.

There are no prohibited therapies during the post-treatment follow-up phase.

Please refer to country-specific requirements in Appendix 7, Section 10.7.2.

6.5.3 Drug Interactions

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

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

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

No drug interaction is expected between MK-1308A and lenvatinib because of their divergent metabolic pathways. MK-1308A 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).

Lenvatinib has been reported to prolong QT/QTc interval. Avoid coadministration of lenvatinib with medicinal products with a known potential to prolong the QT/QTc interval. If QTc prolonging drugs are medically necessary and an acceptable alternative cannot be substituted, refer to Section 8.3.3 for instruction on increased frequency of ECG monitoring.

6.5.4 Rescue Medications and Supportive Care for MK-1308A and Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.1, Table 8 and Table 9 in Section 6.6.2, and Section 6.6.3. 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 MK-1308A.

Note: If after the evaluation of the event, it is determined not to be related to MK-1308A, the investigator does not need to follow the treatment guidance. Refer to Table 8 and Table 9 in Section 6.6.2 and Guidance for Management of Hepatic Events of Clinical Interest in Section 6.6.3 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)

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

Participants who interrupt or discontinue 1 drug (lenvatinib, MK-1308A, or pembrolizumab) due to toxicity can continue with the other drug until criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression). Refer to Section 6.6.5 for dose modification guidance for overlapping toxicity for the MK-1308A plus lenvatinib combination.

6.6.1 [redacted] and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for [redacted] Pembrolizumab Monotherapy, [redacted] or IO Combinations

AEs associated with pembrolizumab monotherapy, [redacted], or IO combination exposure may [redacted]. These [redacted] may occur shortly after the [redacted] pembrolizumab monotherapy, [redacted] or IO combination treatment and may [redacted] Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most [redacted] pembrolizumab monotherapy, [redacted] or IO combination [redacted]. For suspected [redacted], 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.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, [redacted] or IO combinations, pembrolizumab monotherapy, [redacted] or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for [redacted] Adverse Events.

In these cases where the toxicity is attributed to pembrolizumab [redacted] or IO combinations, reinitiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, [redacted] or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, [redacted] or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, [redacted] or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for [redacted], pembrolizumab

monotherapy, [redacted], or IO combinations may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for [redacted] Pembrolizumab Monotherapy, [redacted] or IO Combinations are provided in Table 6. Dose modification, diagnosis, and management guidance for [redacted] is provided in Section 6.6.4.

Table 6 Dose Modification and Toxicity Management Guidelines for CCI Associated With Pembrolizumab Monotherapy, CCI or IO Combinations

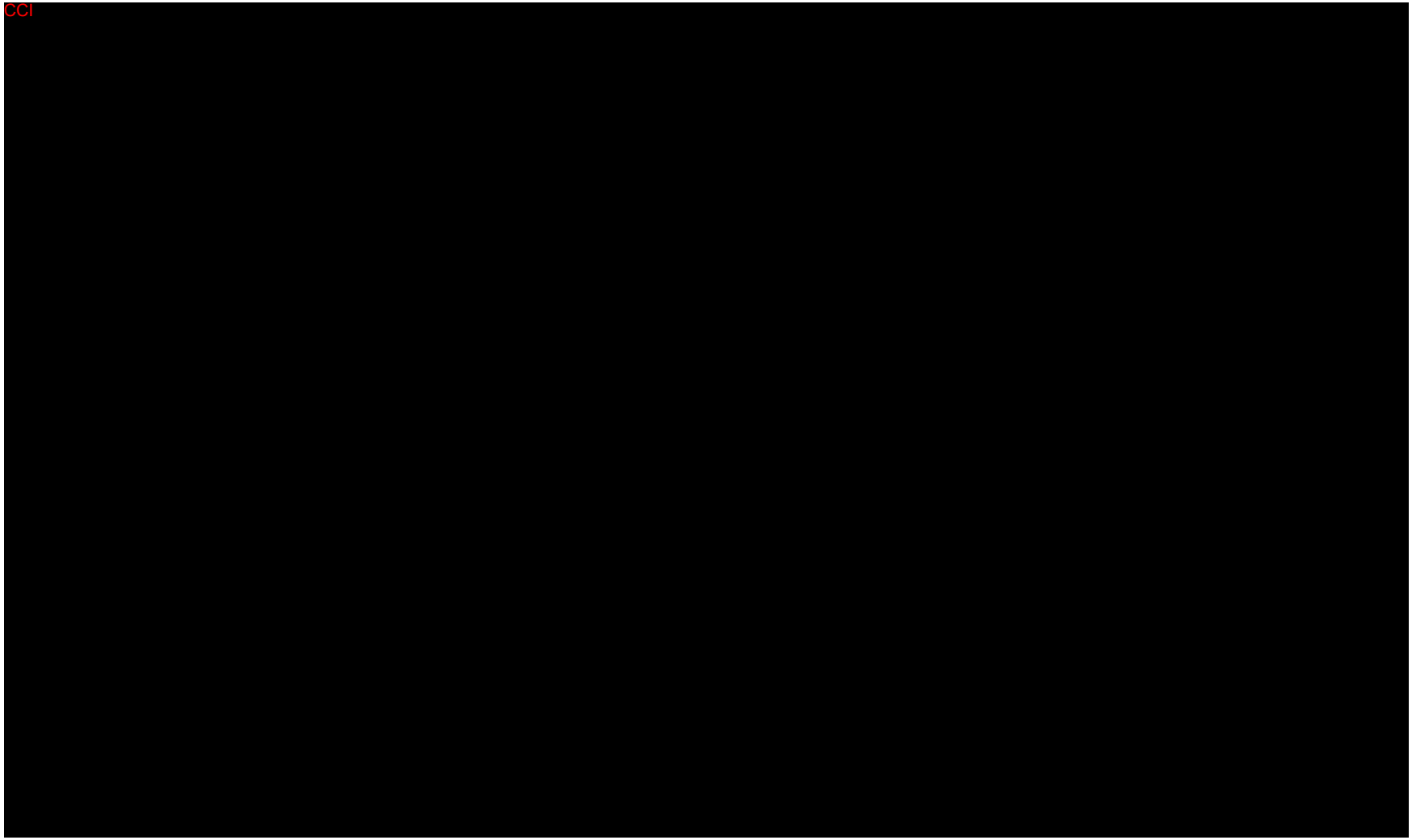
General instructions:

1. Severe and life-threatening CCI
2. CCI
3. CCI
4. CCI

CCI .

CCI

CCI



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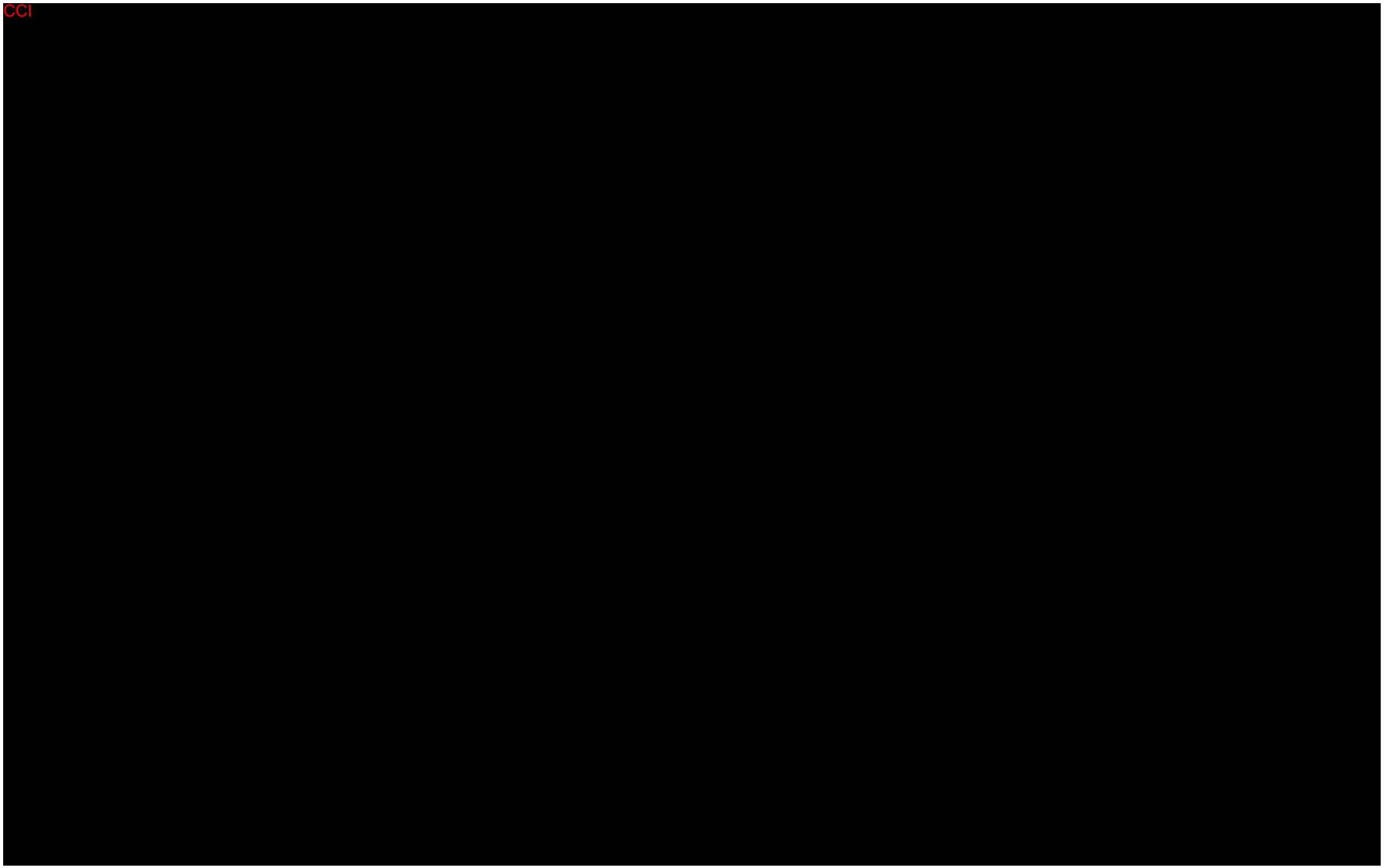


CCI

Dose Modification and Toxicity Management of [redacted]

MK-1308A may cause [redacted]. Signs and symptoms usually develop [redacted]

Dose modification and toxicity management guidelines on [redacted] are provided in Table 7.

Table 7 [redacted] Dose Modification and Treatment Guidelines

NCI CTCAE v5.0 Grade	Treatment	Premedication at Subsequent Dosing
[redacted]		

NCI CTCAE v5.0 Grade	Treatment	Premedication at Subsequent Dosing
CCI [redacted]		

CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI= National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug.
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE, V5.0) at http://ctep.cancer.gov

Other Allowed Dose Interruption for MK-1308A

MK-1308A may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 6 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.2 Lenvatinib Dose Modification

Lenvatinib dose reduction and interruption for participants who experience MK-1308A/lenvatinib combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 8. An interruption of study intervention for more than 28 days will require communication with the Sponsor before treatment can be resumed.

The starting dose of lenvatinib is 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally qd. Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg qd, and 4 mg QoD) per Table 8. 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, communication with the Sponsor is required to increase the dose.

Table 8 Dose Modification Guidelines for Lenvatinib-related Adverse Events

	Adjusted Dose to be Administered		
Initial Lenvatinib Dose (mg, qd)	**Reduction 1**	**Reduction 2**	**Reduction 3**
12 mg qd	8 mg qd	4 mg qd	4 mg QoD
8 mg qd	4 mg qd	4 mg QoD	Discontinue
qd=once daily; QoD=every other day.			

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), thromboembolic events (Section 6.6.2.4), PRES/RPLS (Section 6.6.2.5), hypocalcemia (Section 6.6.2.6), hemorrhage (Section 6.6.2.7), gastrointestinal perforation or fistula formation (Section 6.6.2.8), QT prolongation (Section 6.6.2.9), and osteonecrosis of the jaw (Section 6.6.2.10), as appropriate, before consulting the dose modification table (Table 9). For overlapping toxicities of MK-1308A and lenvatinib please refer to Section 6.6.5.

Table 9 Dose Modification Guidelines for Lenvatinib-related Adverse Events (for the MK-1308A/Lenvatinib Combination)

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,e] or Grade 3[d,e,f]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib by 1 more dose level
Third occurrence[g] (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discontinue lenvatinib
Grade 4[h]: Discontinue Lenvatinib		

AE=adverse event; BMI=body mass index; CTCAE=Common Terminology Criteria for Adverse Events; qd=every day.
Note: For grading see CTCAE v5.0. Collect all AE grades (ie, decreasing and increasing CTCAE grades).

[a] An interruption of study intervention for more than 28 days will require communication with the Sponsor before intervention can be resumed.

[b] Initiate optimal medical management for nausea, vomiting, hypothyroidism, and/or diarrhea before any study intervention interruption or dose reduction.

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

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

[e] Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator.

[f] For Grade 3 thromboembolic event, permanently discontinue lenvatinib. See Section 6.6.2.4.

[g] Not applicable for participants who start at 8 mg qd.

[h] Excluding laboratory abnormalities judged to be nonlife-threatening, in which case manage as Grade 3. For asymptomatic Grade 4 laboratory abnormalities, such as elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.

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 allocated 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,Table 1). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

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

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

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

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

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

1. Continue study intervention 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 intervention can be continued without dose modification.

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

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

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

1. Institute appropriate medical management

2. Discontinue Lenvatinib

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:

Grading of Proteinuria

Grading of proteinuria according to CTCAE v5.0 will be based on the 24-hour urinary protein result if available. If the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria.

Management of Proteinuria

- Management of lenvatinib administration will be based on the grade of proteinuria according to Table 9.

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 UPCR test is required in the following situations:
   - The first (initial) occurrence of ≥2+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while the participant is receiving lenvatinib.
   - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level.
   - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL).
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.

Monitoring

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.
- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

6.6.2.3 Management of Diarrhea

An antidiarrheal agent should be recommended to the participant at the start of lenvatinib and participants should be instructed and educated to initiate antidiarrheal treatment at the first onset of soft bowel movements. The choice of antidiarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 9 should be followed.

6.6.2.4 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 9 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

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

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

PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 9 should be followed.

6.6.2.6 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 v5.0, using the following formula:

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

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

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

6.6.2.7 Management of Hemorrhage

Instructions in Table 9 (Nonhematologic Toxicities) 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.

Participants requiring variceal banding during study treatment period must hold lenvatinib therapy for at least 28 days after the procedure.

6.6.2.8 Management of Gastrointestinal Perforation or Fistula Formation

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

6.6.2.9 Management of QT Prolongation

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

6.6.2.10 Management of Osteonecrosis of the Jaw

Perform an oral examination before treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgment of adequate resolution (See Section 6.6.6).

6.6.3 Definition of Dose-limiting Toxicity

All toxicities will be graded using NCI CTCAE v5.0 based on the investigator assessment.

Dose-limiting toxicities will be defined from toxicities observed during the first cycle of the Safety Lead-in Phase. The occurrence of any of the following toxicities will be considered a DLT unless the investigator assessment determines the toxicity to be clearly not related to the study intervention:

- Any Grade 4 nonhematologic toxicity (not laboratory)
- Any Grade 4 hematologic toxicity lasting >7 days
  - Grade 4 lymphopenia lasting ≥21 days
- Grade 3 platelet count decreased if associated with clinically significant hemorrhage
- Any Grade 3 nonhematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care

- Any clinically significant Grade 3 or Grade 4 nonhematologic laboratory abnormality (except AST/ALT/GGT) if:
  - medical intervention is required to treat the participant, or
  - the abnormality leads to hospitalization, or
  - the abnormality persists for >1 week (or bilirubin if persists >4 weeks)
- AST/ALT >10.0×ULN OR > 10.0x baseline if baseline > ULN, which does not resolve within 1 week, or else is clinically symptomatic
- Any febrile neutropenia Grade 3 or Grade 4
- Any treatment-related AE that causes the participant to discontinue study intervention during the DLT window
- Any Grade 5 toxicity

See country-specific requirements in Appendix 7, Section 10.7.2.

6.6.4 Guidance for Management of Hepatic Events of Clinical Interest

Hepatic ECIs include any of the following events if the events are considered not due to disease progression as judged by the investigator. All of these events (if not associated with disease progression under study) will require holding study intervention and notification of the event(s) to the Sponsor within 24 hours after awareness via electronic media or paper.

For dose interval modification, refer to Section 6.6.1 and 6.6.2.

- ALT:
  - Among participants with Baseline ALT <2×ULN: ALT ≥5×ULN
  - Among participants with Baseline ALT ≥2×ULN: ALT >3× the Baseline level
  - ALT >500 U/L regardless of baseline level
- Total bilirubin:
  - Total bilirubin >3.0 mg/dL
- Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
  - New onset clinically detectable ascites requiring intervention for >3 days
  - Hepatic encephalopathy
  - Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)

All cases of retreatment after interruption of study intervention for HECI must be recorded in the database. HECIs are not the result of disease progression, and therefore the following evaluations are not required for these etiologies.

Immediate assessment in case of HECI:

All Participants

- All participants should be considered for evaluation according to the directions below within 72 hours of the alert for a nonoverdose ECI. Laboratory assessments of HECIs will be performed locally; central laboratory is acceptable if local laboratory is not available.
- Procedures:
  - Consider obtaining a consultation with a hepatologist
  - Obtain a workup for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus
  - Assess for ingestion of drugs/supplements with hepatotoxic potential
  - Assess for alcohol ingestion
  - Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
  - Repeat ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, INR, and complete blood count with differential
  - Measure HCV RNA viral load (applies only for participants who have current active HCV infection or had infection in the past)
  - HBV DNA, HBsAg, anti-HBc (total and IgM), and anti-HBs regardless of prior HBV status (Note: participants should be questioned about compliance with the use of antiviral agents)
  - Other laboratories or imaging studies as clinically indicated
  - Consider liver biopsy if indicated

HCC patients are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC participants in this study. The recommendation is to hold both MK-1308A and lenvatinib interventions and initiate “Management of HECI for Lenvatinib Toxicity”. If toxicity does not improve within 1 to 2 days or worsens, follow “Management of HECI for MK-1308A” below.

6.6.4.1 Management of HECI for Lenvatinib Toxicity

Instructions for dose reductions or interruptions for lenvatinib are shown in Table 10.

Table 10 Lenvatinib Dose Reduction and Interruption Instructions

Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QoD]). Any dose reduction below 4 mg QoD must be discussed with the Sponsor. Once the dose has been reduced, it cannot be increased at a later date.		
Lenvatinib Induced HECI	**Management**	**Dose Adjustment**
First occurrence	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 dose level.
Second occurrence (same toxicity or new toxicity)	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 more dose level.
Third occurrence (same toxicity or new toxicity)[a]	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 more dose level.
Fourth occurrence (same toxicity or new toxicity)	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Discontinue lenvatinib.
HECI=hepatic events of clinical interest. [a] Not applicable for participants who start at 8 mg qd.		

6.6.4.2 Management of CCI [redacted]

Instructions for management of CCI [redacted] are shown in Table 11.

Table 11 Management of CCI [redacted]

	Diagnosis	Management
CCI [redacted]		

	Diagnosis	Management
CCI	[redacted]	

6.6.5 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of MK-1308A and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the others. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for MK-1308A treatment. However, certain

AEs, such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study intervention. Therefore, evaluation of attribution is important for determining the study intervention 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 MK-1308A is dosed q6w due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

   - If an AE is identified during a treatment cycle (ie, between 2 MK-1308A 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 MK-1308A 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.

The same dose modification guidelines should be followed for pembrolizumab as for MK-1308A.

6.6.6 Other Allowed Dose Interruptions for Lenvatinib

If the participant is receiving treatment with lenvatinib and requires surgical procedure 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) before the surgical procedure and then restart it at least 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.

6.7 Intervention After the End of the Study

On study completion, participants are to be discontinued and may be enrolled in an extension study, if available.

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Not applicable.

6.9.1 Study Site Retention Samples

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.10.3 unless the participant has withdrawn from the study as described in Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1.2 (exception if the Sponsor approves treatment continuation).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Participant has any of the following nonoverdose hepatic ECIs:
    - ALT >20×ULN (confirmed within 1 week)
    - Drug-related total bilirubin >10 x ULN
    - CP score of >9 points if not improved to CP score <9 by intervention within 3 days
    - Hepatic encephalopathy not manageable by therapy within 3 days
    - If ascites is not manageable by intervention within 3 days

- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related

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

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

Informed consent given by the participant (or their legally acceptable representative) must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or their legally acceptable representative) and of the person conducting the consent discussion.

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

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

Specifics about the study and the study population are to be included in the ICF.

The participant (or their legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

8.1.2 Inclusion/Exclusion Criteria

As of Amendment 6, this section of text is kept for historical reasons.

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

As of Amendment 6, this section of text is kept for historical reasons.

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

8.1.4 Medical History

As of Amendment 6, this section of text is kept for historical reasons.

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

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

For all participants with a history of hepatitis B or hepatitis C, information on past and/or present antiviral treatment will be collected.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1.

8.1.7 Assignment of Allocation Number

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

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

8.1.8 Study Intervention Administration

As of Amendment 6, text pertaining to study intervention administrations of MK-1308A and pembrolizumab is kept in this section for historical reasons. Currently, all participants are on lenvatinib monotherapy, which is standard of care for this patient population.

Administration of MK-1308A will be witnessed by the investigator and/or study staff and/or qualified designee per institutional guidelines and procedures. Lenvatinib may be administered at home. Please refer to Section 8.1.8.1 for further detail.

Every effort should be made to begin study intervention on the day of allocation. However, study intervention may begin up to 3 days following allocation if there are unforeseen circumstances.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 MK-1308A

MK-1308A will be administered as a 30-minute IV infusion on Day 1 of the cycle q6w. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes –5 min/+10 min).

After Cycle 1 Day 1, MK-1308A may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

8.1.8.1.2 Pembrolizumab (if MK-1308A is Discontinued)

Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of the cycle q6w. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

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

8.1.8.1.3 Lenvatinib

Lenvatinib is provided as 4-mg capsules. Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) 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, on Day 1 of Cycle 1 and 3, lenvatinib will be administered 0 to 4 hours after completion of MK-1308A administration.

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.

8.1.8.2 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.

8.1.9 Discontinuation and Withdrawal

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

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

As of Amendment 6, all text pertaining to tumor assessments and PROs is kept in this section for historical reasons. PRO is no longer required, and tumor imaging is per standard of care and does not need to be submitted to the BICR vendor.

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the iCRO can be found in the SIM. Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Triple phase imaging of the liver is required, as described in the SIM. Brain imaging is performed as clinically indicated. MRI is the strongly preferred modality for imaging the brain. The same imaging technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment 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.

All scheduled images for all study participants from the sites will be submitted to the iCRO. 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 show radiologic progression, should also be submitted to the iCRO.

8.2.1.1 Initial Tumor Scans

The Screening images must be submitted to the iCRO for prospective review.

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 allocation and can be assessed by the iCRO.

8.2.1.2 Tumor Scans During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the Cycle 1 Day 1. Subsequent tumor imaging should be performed q9w (63 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression per RECIST 1.1 is identified by the investigator (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the iCRO.

Objective response 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.

Per iRECIST (Section 8.2.1.5), disease progression should be confirmed by the site. 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 intervention. Exceptions are detailed in Section 8.2.1.5.

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

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of

discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of Cycle 1 Day 1. Refer to Section 8.2.1.2.

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

- PD as defined by RECIST 1.1
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

8.2.1.4 RECIST 1.1 Assessment of Disease

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

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 to make treatment decisions [Seymour, L., et al 2017]. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic disease progression 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 disease progression, and is not required to have repeat tumor imaging for confirmation of disease progression 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 disease progression 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 disease progression 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 disease progression is confirmed, participants will be discontinued from study intervention.

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

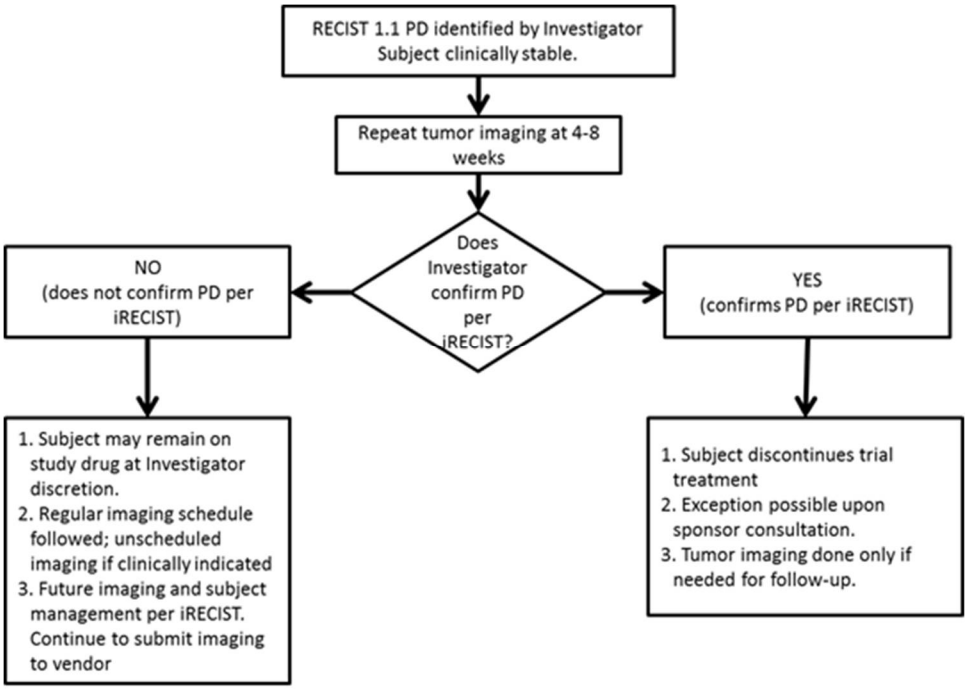
A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 12 and illustrated as a flowchart in Figure 2.

Table 12 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of disease progression by RECIST 1.1 per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm disease progression	May continue study intervention at the assessment of the investigator and after the participant's consent	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms disease progression (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment (exception is possible upon communication with the 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 disease progression. 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 disease progression 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; iPR=iRECIST partial response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.

Figure 2 Imaging and Treatment for Clinically Stable Participants Treated With MK-1308A After First Radiologic Evidence of Disease Progression Assessed by the Investigator



iRECIST=adapted RECIST 1.1 for immune-based therapeutics; PD=progressive disease RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1.

8.2.1.6 Modified RECIST (mRECIST) Assessment of Disease

Modified RECIST for HCC allows evaluation of treatment effects that are not reflected in simple total size changes of lesions. Details are fully described in [Lencioni, R. 2010]. RECIST 1.1 by BICR will still be the primary measure of the tumor response. Extrahepatic lesion assessment, as well as response categories and definitions, are identical to RECIST 1.1. Key differences from RECIST 1.1 include:

- Lesions within the liver parenchyma are measured so as to include only the portion showing increased contrast enhancement in the arterial phase.
- New lesions in the liver must meet one of the following conditions to be considered indicators of progression:
  - At least 10 mm in longest diameter, and showing typical HCC enhancement (enhancement during the arterial phase and washout during the portal venous phase)
  - At least 10 mm in longest diameter with atypical enhancement, but showing at least 10 mm of growth on a subsequent scan
- Porta hepatis lymph nodes should never be selected as target lesions, and should only be followed as nontarget lesions if their short axis measurement at Screening is ≥20 mm.

8.2.2 Patient-reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D-5L questionnaires will be administered by trained site personnel and completed by participants in the following order: EORTC QLQ-C30, EORTC QLQ-HCC18, and then EQ-5D-5L. See SoA (Section 1.3) for PRO administration schedule.

It is best practice and strongly recommended that PROs are administered to allocated participants before drug administration, AE evaluation, and disease status notification. If the participant does not complete the PROs 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 allocation of a participant, the translated version of the PROs are not available for that language/country, and therefore cannot be completed by the participant at Cycle 1 Day 1, the PRO should still be completed at the time point during the study once the translated version becomes available.

NOTE: For some sites, the translated EORTC QLQ-C30 and/or EORTC QLQ-HCC18 might become available after study startup and should be administered to participants at their time of allocation; for some sites, the EORTC QLQ-C30 and/or EORTC QLQ-HCC18 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.

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 during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examinations are described in Section 1.3. Assessment for possible ascites and hepatic encephalopathy should be noted on every examination. 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 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 study intervention administration. Assessment for possible ascites and hepatic encephalopathy should be noted on every examination. 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], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in the SoA (Section 1.3) by a validated method.

- Blood pressure and pulse will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.
- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) shows an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.
- At the C1D8 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

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 Section 1.3) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Medicinal products with a known potential to prolong the QT/QTc interval (including Class Ia and III antiarrhythmics) must be used cautiously. Refer to the lenvatinib prescribing information.

8.3.4 Echocardiogram or Multiple Gated Acquisition Scan

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

8.3.5 Child-Pugh Score

As of Amendment 6, the text below is kept for historical reasons, but Child-Pugh score assessments are to be performed per standard of care.

Originally developed in 1973, the Child-Pugh score was used to estimate the risk of operative mortality in participants 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, total bilirubin 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).

8.3.6 Clinical Safety Laboratory Assessments

As of Amendment 6, the text below is kept for historical reasons, but laboratory tests are to be performed per standard of care.

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

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

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

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- 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 90 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

8.3.6.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Complete blood count with differential and clinical chemistry (except for lipase) results must be reviewed before administration of study intervention. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting study intervention.

8.3.7 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine and/or serum) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine and/or serum) should be conducted as per SoA for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for participant's contraception as noted 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.

8.3.8 Performance Assessments

8.3.8.1 Eastern Cooperative Oncology Group Performance Status

As of Amendment 6, the text below is kept for historical reasons, but assessments of ECOG performance status are to be performed per standard of care.

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 (see Appendix 9) at screening, before the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

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

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

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, 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 through 90 days, or 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 120 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through 120 days after MK-1308A, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time 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 the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 13, Table 14 and Table 15.

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

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

	Reporting Time Period: Within 24 hours of Learning of Event		
Type of Event	**Consent to Randomization/Allocation [a]**	**Randomization/ Allocation through Protocol-specified Follow-up Period**	**After the Protocol-specified Follow-up Period**
SAE	Report if: • due to protocol-specified intervention • causes exclusion • participant is receiving placebo run-in or other run-in treatment	Report all events	Report if: • related to study intervention (Follow ongoing to outcome)
Cancer New cancer excluding metastases or progression of the cancer under study • meeting serious criteria	Report if: • due to protocol-specified intervention • causes exclusion • participant is receiving placebo run-in or other run-in treatment	Report all events	Report if: • related to study intervention (Follow ongoing to outcome)
Pregnancy/Lactation Exposure	Report if: • participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial Screening is not a reportable event unless the participant has received study intervention.	Report all events	If previously reported: • Follow to completion/ termination; report outcome
ECI (requiring regulatory reporting)	Report if: • due to intervention • causes exclusion	Report if: • HECI • requiring regulatory reporting	Not required

ECI=event of clinical interest; HECI=hepatic events of clinical interest; SAE=serious adverse event.
[a] From the provision of documented informed consent onward.

Table 14 Reporting Progression of the Cancer Under Study and/or New Cancer Events

Event	Reporting Time Period: 5 days of Learning of the Event	
	Consent to Randomization/ Allocation	**Randomization/ Allocation through Protocol-specified Follow-up Period**
Progression of the cancer under study	Report if: • due to protocol-specified intervention • causes exclusion • participant is receiving placebo run-in or other run-in treatment	Not reported
New cancer that does not meet serious criteria, excluding metastases or progression of the cancer under study	Report if: • due to protocol-specified intervention • causes exclusion • participant is receiving placebo run-in or other run-in treatment	Report all

Table 15 Additional Reportable Events and Time Period to Report

Type of Event	Reporting Time Period:			Time Frame to Report Event and Follow-up Information to Sponsor:
	Consent to Randomization/ Allocation	**Randomization/ Allocation through Protocol-specified Follow-up Period**	**After the Protocol-specified Follow-up Period**	
ECI (not required by regulatory reporting)	Report if: • due to protocol-specified intervention • causes exclusion	Report any: • non-HECI • not required by regulatory reporting	Not required	Within 5 calendar days of learning of event
Overdose	Report if: • participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Within 5 calendar days of learning of event
Nonserious AEs	Report if: • due to protocol-specified intervention • causes exclusion	Report all	Not required	Per data entry guidelines

AE=adverse event; ECI=event of clinical interest; HECI=hepatic events of clinical interest.

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

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 (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

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

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

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born

with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

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

For country-specific requirements see Appendix 7.

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/designee will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon 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

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results. Lenvatinib overdose without an associated AE is not considered an ECI.

2. Hepatic ECIs as defined in Section 6.6.4. All of these events (if not associated with disease progression under study) will require holding study intervention, notification of the event(s) to the Sponsor within 24 hours after awareness via electronic media or paper.

For dose interval modification, refer to Section 6.6.1 and 6.6.2. For guidance related to the diagnosis and management of hepatic ECIs, refer to Section 6.6.4.

8.5 Treatment of Overdose

CCI
CCI

CCI [redacted] An overdose of lenvatinib will be defined as any dose ≥20% over the prescribed dose described in the protocol.

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, RCC, and HCC.

No specific information is available on the treatment of overdose of MK-1308A or lenvatinib.

All reports of MK-1308A 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 MK-1308A 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

As of Amendment 6, the text below is kept for historical reasons, but samples for analysis of pharmacokinetics are no longer collected.

8.6.1 Blood Collection for Serum Quavonlimab and Pembrolizumab and Plasma Lenvatinib

8.6.1.1 Plasma Collection for Lenvatinib PK

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

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

Lenvatinib PK plasma samples may be disposed of in accordance with sample destruction procedures once PK data are finalized.

8.6.1.2 Serum Collection for Quavonlimab and Pembrolizumab PK and ADA

Serum 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 and ADA samples will be provided in the Laboratory Manual. Simultaneous PK sampling is required for interpretation of ADA analysis.

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

PK and ADA samples may be disposed of in accordance with sample destruction procedures once PK and ADA data are finalized.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

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

Approximately 28 days before treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Documented informed consent must be obtained before performing any protocol-specific procedure. Results of a test performed before the participant providing documented informed consent as part of routine clinical management are acceptable in lieu of a Screening test if performed within the specified time frame. 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. Exceptions are hepatitis testing, AFP, and thyroid testing, which may be performed up to 28 days before the first dose of study intervention.
- Evaluation of ECOG is to be performed within 7 days before the first dose of study intervention.
- For WOCBP, 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).
- Tissue is not required for allocation, however submission of archival tissue is strongly encouraged, if available. Formalin-fixed, paraffin-embedded block specimens are preferred to slides.

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.

8.10.2 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 Posttreatment Visit

8.10.3.1 Safety Follow-up Visit

Safety Follow-up will occur during 2 separate visits: 30 days AND 90 days after last dose. One 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 End-of-Treatment Visit occurs ≥30 days from last dose of study intervention, the 30-day Safety Follow-up Visit is not required. In this situation, all procedures required at both the End-of-Treatment Visit and the 30-day Safety Follow-up Visit should be performed at the End-of-Treatment Visit. End-of-Treatment is defined as the date when the participant discontinues all study interventions.

For participants continuing with imaging follow-up at ≥9W, if their 90-day Safety Follow-up Visit falls within the same window as their imaging follow-up visit, these visits may be combined. All procedures required at the Safety Follow-up Visit at 90 days will be performed at the imaging follow-up at ≥9W.

8.10.3.2 Efficacy Follow-up Visits

As of Amendment 6, the text below is kept for historical reasons, but efficacy follow-up visits should be performed per standard of care.

Participants who discontinue study intervention for a reason other than disease progression will move into the Efficacy Follow-up Phase and should be assessed q9w to monitor disease status; if a clinic visit is not feasible, the participant may be contacted by telephone or e-mail. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, or end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

All participants who discontinue study intervention before disease progression will continue to undergo tumor assessments q9w in the Efficacy Follow-up Period until disease progression is documented or a new anticancer therapy is initiated, unless the participant withdraws consent. After the primary analysis for the study, tumor assessments should be performed q9w or more frequently per local standard of care.

8.10.3.3 Survival Follow-up Contacts

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

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

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

8.10.4 Vital Status

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

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 primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in an sSAP and referenced in the CSR for the study. Other planned analyses (ie, those specific to the analysis of PK data or PROs) will be documented in the sSAP or separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Phase 2, Multicenter, Clinical Study to Evaluate the Safety and Efficacy of MK-1308A (Coformulated MK-1308/MK-3475) in Combination with Lenvatinib (E7080/MK-7902) in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma
Treatment Assignment	Approximately 110 participants will be allocated to Dose Level 0; up to 10 participants might be allocated to an alternative dose. This is a nonrandomized open-label study.
Analysis Populations	Efficacy: APaT and received the Dose Level 0 Safety: APaT; DLT-evaluable population for DLT analysis
Primary Endpoints	Efficacy: ORR per RECIST 1.1 by BICR Safety: DLT (Safety Lead-in Phase only); AEs, SAEs, irAEs, and hepatic AEs; study drug discontinuations due to AEs
Statistical Methods for Key Efficacy Analyses	The point estimate of ORR and 95% CI using exact binomial method by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934] will be provided.
Statistical Methods for Key Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate.
Interim Analyses	Efficacy: No interim efficacy analyses are planned for this study. Safety: The first safety IA will be performed and reviewed when the first 20 participants on Dose Level 0 from Safety Lead-in Phase or Efficacy Expansion Phase have been treated and had their 6-week visit. Afterwards, safety data will be reviewed periodically in the study.
Multiplicity	No multiplicity adjustment is planned in this study.
Sample Size and Power	The planned sample size is approximately 110 participants on Dose Level 0. Section 9.9 provides the precision of the ORR estimates.

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 a nonrandomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is allocated and treatment is assigned.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

9.4 Analysis Endpoints

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

9.4.1 Efficacy Endpoints

Primary

- **Objective Response Rate**

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

Secondary

- **Duration of Response**

For participants who demonstrate confirmed CR or PR per RECIST 1.1 assessed by BICR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. See Section 9.6.1.2 for definition of censoring.

- **Disease Control Rate**

DCR is defined as the proportion of participants who have achieved CR, PR, or SD after ≥6 weeks (the start of the window for the first scheduled scan) per RECIST 1.1 assessed by BICR.

- **Progression-free Survival**

PFS is defined as the time from the first dose of study intervention to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. See Section 9.6.1.4 for definition of censoring.

- **Time to Progression**

TTP is defined as the time from the first dose of study intervention to the first documented disease progression per RECIST 1.1 assessed by BICR. See Section 9.6.1.5 for definition of censoring.

- **Overall Survival**

OS is defined as the time from the first dose of study intervention to death due to any cause.

- **ORR**, **DOR**, **DCR**, **PFS** and **TTP** per mRECIST assessed by BICR.

Exploratory

- **ORR**, **DOR**, **DCR**, **PFS** and **TTP** per RECIST 1.1 and iRECIST assessed by investigator.

9.4.2 Safety Endpoints

The primary safety endpoint is the incidence of DLTs (for Safety Lead-in Phase), and safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests and vital signs. Safety parameters to be analyzed include, but are not limited to, AEs, SAEs, fatal AEs, and laboratory changes. Definition of DLTs is described in Section 6.6.3. Hepatic AEs are defined by the HECIs criteria, as provided in Section 6.6.4. Safety measurements are described in Section 4.2.1.2 and Section 8.

9.4.3 Patient-reported Outcome Endpoints

HRQoL will be assessed using the global score of the EORTC QLQ-C30 and EORTC QLQ-HCC18. TTD will be evaluated using EORTC QLQ-C30 and EORTC QLQ-HCC18 global health status/QoL. Health status and health utilities will be assessed using the EQ 5D-5L. Additional details will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

Efficacy analyses will be conducted in the APaT population who start therapy at Dose Level 0, that is all allocated participants who received at least 1 dose of study intervention at Dose Level 0 from the Safety Lead-in Phase and the Efficacy Expansion Phase.

For the analyses of DOR, the subset of participants who show a confirmed CR or PR will be included in the analysis population.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all allocated participants who received at least one dose of study intervention. Participants will be analyzed separately by the dose received.

The DLT-evaluable population includes APaT participants that meet the criteria for DLT evaluability (ie, finished DLT evaluation period without a DLT or experienced a DLT in the DLT evaluation period). See Section 4.1.1, Section 5.5 and Section 6.6.3 for details.

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

9.5.3 Patient-reported Outcome Analysis Populations

The PRO analyses are based on the PRO FAS population, defined as participants who have at least 1 PRO assessment available for the specific endpoint and have received at least 1 dose of the study intervention.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP. The primary assessment of efficacy endpoints will be based on BICR per RECIST 1.1, and supportive analyses will be performed using BICR per mRECIST, and investigator's assessment per RECIST 1.1 and iRECIST.

9.6.1.1 Objective Response Rate

The point estimate of ORR will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. Participants in the analysis population (APaT) with missing response data are considered as participants without OR.

9.6.1.2 Duration of Response

The nonparametric Kaplan-Meier method will be used to estimate the DOR curve, and median estimate from the Kaplan-Meier curve will also be provided. Only the subset of participants who show a confirmed CR or PR will be included in this analysis.

Censoring rules for DOR are summarized in Table 16.

For DOR analysis, a corresponding summary of the reasons the responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up,

and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 16 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (nonevent)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (nonevent)
Death or progression immediately after ≥2 consecutive missed disease assessments without further valid non-PD disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (nonevent)
Death or progression after ≤ 1 missed disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)
Abbreviations: DOR=duration of response; PD=progressive disease. A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

9.6.1.3 Disease Control Rate

For DCR, the point estimate and 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. Participants in the analysis population (APaT) with missing response data are considered as participants whose disease is not under control.

9.6.1.4 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve, and median estimate from the Kaplan-Meier curve will also be provided.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a PD event.

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

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers discontinuation of treatment due to reasons other than CR or initiation of new anticancer treatment, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analyses are summarized in Table 17.

Table 17 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥2 consecutive missed disease assessments without further valid non-PD disease assessments or after new anticancer therapy, if any	Censored at the earlier date of 1) the last disease assessment prior to the ≥2 consecutive missed disease assessment and 2) the last disease assessment prior to the new anticancer therapy, if any. In a special case of participants without postallocation scans who died later than after ≥2 consecutive missed disease assessments or started new anticancer therapy, the PFS will be censored on the allocation date	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer therapy is not initiated	Censored at last disease assessment. In a special case of participants without postallocation scans, the PFS will be censored on the allocation date	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study or completed study therapy
No PD and no death; new anticancer therapy is initiated	Censored at last disease assessment before new anticancer therapy. In a special case of participants without postallocation scans who started new anticancer therapy, the PFS will be censored on the allocation date	Censored at last disease assessment	Progressed at date of new anticancer therapy
Abbreviations: PD=progressive disease; PFS=progression-free survival.			

9.6.1.5 Time to Progression

The nonparametric Kaplan-Meier method will be used to estimate the TTP curve, and median estimate from the Kaplan-Meier curve will also be provided.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR, regardless of discontinuation of study drug. Unlike the PFS analysis, death is not considered an event. Censoring rules for TTP are summarized in Table 18.

Table 18 Censoring Rules for TTP

Situation	Primary Analysis
No PD; new anticancer treatment is not initiated	Censored at last non-PD disease assessment; for those without postallocation scans, censored at allocation
No PD; new anticancer treatment is initiated	Censored at last non-PD disease assessment before new anticancer treatment; for those without postallocation scans, censored at allocation
PD documented after ≤1 missed disease assessment and before new anticancer therapy, if any	Progressed at date of documented PD
PD documented after ≥2 consecutive missed disease assessments without further valid non-PD disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the ≥2 consecutive missed disease assessments; for those without postallocation scans, censored at allocation
Abbreviations: PD=progressive disease; TTP=time to progression.	

9.6.1.6 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curve, and median estimate from the Kaplan-Meier curve will also be provided. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.7 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 19.

Table 19 Analysis Strategy for Key Efficacy Variables

Endpoint/ Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per RECIST 1.1 by BICR	Exact method based on binomial distribution (Clopper-Pearson method)	APaT	Participants with missing data are considered nonresponders
Secondary Analyses			
DOR per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	All responders in APaT	Nonresponders are excluded from analysis. Responders are censored according to the censoring rules in Table 16
DCR per RECIST 1.1 by BICR	Exact method based on binomial distribution (Clopper-Pearson method)	APaT	Participants with missing data are considered as participants whose disease not under control
PFS per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	APaT	Censored according to rules in Table 17
TTP per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	APaT	Censored according to rules in Table 18
OS	Summary statistics using Kaplan-Meier method	APaT	Censored at participant's last known alive date

Abbreviations: APaT=all-participants-as-treated; BICR=blinded independent central review; DCR=disease control rate; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors; TTP=time to progression.

9.6.2 Statistical Methods for Safety Analyses

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

Descriptive statistics (counts and proportion of total participants) will be provided for participants with any AE, a Grade 3-5 AE, a serious AE, a drug-related AE, an AE which is both drug-related and serious, a Grade 3-5 AE which is drug-related, who discontinued due to an AE and death.

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

Dose-limiting toxicities will be listed and summarized. The pool adjacent violators-algorithm [Ji, Y., et al 2007], which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at the RP2D and the 80% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.3 Statistical Methods for Patient-reported Outcome Analyses

Details of PRO analyses will be described in the sSAP.

9.6.4 Demographic and Baseline Characteristics

The number and percentage of participants screened and allocated and the primary reasons for Screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim efficacy analyses are planned for this study. The first safety IA will be performed and reviewed when the first 20 participants on Dose Level 0 from Safety Lead-in Phase or Efficacy Expansion Phase have been treated and had their 6-week visit. Afterwards, safety data will be reviewed periodically in the study.

9.8 Multiplicity

No multiplicity adjustment is planned in this study.

9.9 Sample Size and Power Calculations

In this study, approximately 110 participants will be allocated to the Dose Level 0. Table 20 shows the two-sided 95% confidence interval for ORR with 110 participants for different observed response rates based on the method of Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 20 Two-sided 95% Confidence Interval for ORR With 110 Participants

Number of Observed Responders	ORR Estimates (%)	95% CI of ORR (%)
49	44.5	(35.1, 54.3)
52	47.3	(37.7, 57.0)
55	50.0	(40.3, 59.7)
58	52.7	(43.0, 62.3)

Abbreviations: CI=confidence interval; ORR=objective response rate.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the ORR will be estimated within each category of the following subgroup variables:

- Age category (≤65 vs >65 years)
- Sex (female vs male)
- Race (white vs all others)
- Region (US vs non-US)

- Alpha fetoprotein (AFP) (>400 ng/mL vs ≤400 ng/mL)
- Macrovascular invasion (yes vs no)
- Extrahepatic disease (yes vs no)
- ECOG PS (0 vs 1)
- ALBI Grade (1 vs 2+)
- Etiology (uninfected vs infected (HCV or HBV positive))

A forest plot will be produced, which provides the point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above. If the number of participants in a category of a subgroup variable is less than 10% of the APaT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of Exposure for a participant is defined as the number of cycles and number of days in which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the overall study intervention, and for individual treatment components for the APaT population. Further details will be provided in the sSAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

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

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.1.3 Data Protection

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

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

The participant must be informed that 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 before transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee (SAC)

This study was developed in collaboration with an SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include 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 ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.10 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

All laboratory assessments are kept in this section for historical reasons. Laboratory assessments are to be performed per standard of care as of Amendment 6.

- The tests detailed in Table 21 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 21 Protocol-required Clinical Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
	RBC Count			
	Hemoglobin			
	Hematocrit			
Chemistry	Sodium	Potassium	Chloride	Carbon dioxide (CO_2 or Bicarbonate)[a]
	Blood Urea Nitrogen (BUN)[b]	Creatinine[c]	Glucose	Calcium
	Total Protein	Albumin	Total bilirubin and direct bilirubin[d]	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)
	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Alkaline phosphatase	Magnesium	Phosphorous
	Amylase	Lipase[e]	Lactate Dehydrogenase	Triglycerides
	GGT			
Urinalysis/ Urine dipstick testing	• Specific gravity • pH, glucose, protein, blood (or hemoglobin), ketones, by dipstick[f]			

Laboratory Assessments	Parameters
Other Tests	• Serology: Anti-HCV (IgG), HCV viral load, HCV genotype, anti-HBs, HBsAg, Anti-HBc (total and IgM), HBV viral load[g] • PT/INR • AFP • Serum or urine pregnancy test • Thyroid-stimulating hormone (TSH)[h], Free thyroxine (FT4)[h], Triiodothyronine (T3)[h] • Serology HIV antibody as required by local health authority or institutional regulations.

AFP=alpha fetoprotein; Anti-HBc=antihepatitis B core antibody; Anti-HBs=antihepatitis B surface antibody; GFR=glomerular filtration rate; GGT=gamma-glutamyl transferase; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; PT=prothrombin time; RBC=red blood cells; ULN=upper limit of normal; WBC=white blood cells.

[a] Performed only if considered local standard of care.

[b] Urea is acceptable if BUN is not available as per institutional standard.

[c] GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.

[d] Perform only if total bilirubin is above ULN.

[e] After Cycle 1, retrospective review of lipase results is allowed when the results are not available before dosing.

[f] If urine protein is ≥2+ or ≥100 mg/dL (first occurrence or a subsequent increase in severity of urine dipstick proteinuria or urinalysis occurring on the same lenvatinib dose level), then a 24-hour urine collection should be performed to quantify the 24-hour urine protein excretion.

[g] All study-required laboratory assessments will be performed by a local laboratory. Additionally, hepatitis testing (Anti- HCV [IgG], HCV viral load, HCV genotype, anti-HBs, HBsAg, Anti-HBc [total and IgM], HBV viral load) may be performed centrally.

[h] Free T4, T3, and TSH levels will be performed as indicated in Section 1.3 (SoA). T3: T3 is preferred; if not available, Free T3 may be tested. There may be instances when sites are unable to obtain the thyroid function testing results before scheduled dosing. After Cycle 1, review of thyroid function test results after dosing is acceptable. Results must be available and reviewed before the next scheduled visit.

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Lenvatinib overdose without an associated AE is not reportable as an AE. Refer to Section 8.5 for the definition of overdose.

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

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

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

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

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, v5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
    - Grade 4: Life-threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.

Assessment of causality

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

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT

RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

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

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

SAE reporting to the Sponsor via paper CRF

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

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

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the 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 allocation.

10.5.2 Contraceptive Requirements

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

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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 China

Section 8.8 Biomarkers

China sites may allocate participants on the protocol without submitting biomarker samples, including tissue and blood, until authorization is obtained from Human Genetics Resources Administration of China to collect these biomarker samples.

10.7.2 Japan

Section 4.1 Overall Design

The safety and tolerability of the combination of MK-1308A and lenvatinib, and the PK of quavonlimab/pembrolizumab in Japanese participants will be evaluated at the recommended dose of the MK-1308A and lenvatinib combination determined in the Safety Lead-in Phase.

Japan has country-specific requirements for the protocol that are summarized below:

Section 1.3 Schedule of Activities

- For assistance with early diagnosis of pneumonitis/interstitial lung disease in study participants, SpO_2 will be added at the time of vital sign assessments.

- Quavonlimab/pembrolizumab PK blood serum samples will also be collected on C1D8, C3D8, C4D1, C6D1, C7D8, and C8D1. Collection times for additional PK samples should be aligned as close to the time of sample collection at predose on C1D1 as possible. There is no restriction on the administration time of lenvatinib for collecting additional samples.

- Quavonlimab/pembrolizumab ADA blood serum samples will also be collected on C4D1 and C6D1.

Table 22 Schedule of Activities

	Screen-ing	Treatment Period 21-Day Cycles													EOT	Posttreatment			Notes
Intervention Cycles/ Titles		**1**			**2**		**3**		**4**	**5**	**6**	**7**		**8 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**8**	**1**	**1**	**1**	**1**	**8**	**1**	**At D/C**	**Safety FU[a,b]**	**Efficacy FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to -1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**± 7**	**Q9W (± 7)**	**Q12W (± 7)**	
Vital signs (resting BP, pulse, RR, temp, and pulse oximetry [SpO2]) and weight	X	X	X	X	X	X	X		X	X	X	X		X	X	X			C1D8, C1D15, and C2D15 clinic visits are mandatory only during the Safety Lead-in Phase. During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required.

	Screen-ing	Treatment Period 21-Day Cycles													EOT	Posttreatment			Notes
Intervention Cycles/ Titles		1			2		3		4	5	6	7		8 to last					
Cycle Day		1	8	15	1	15	1	8	1	1	1	1	8	1	At D/C	Safety FU[a,b]	Efficacy FU[c]	Survival FU	
Scheduling Window (Days):	–28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		± 7	Q9W (± 7)	Q12W (± 7)	
Quavonlimab/ Pembro-lizumab PK Serum Sample[d, e]		X	X		X		X	X	X	X	X	X	X	X	X	X			Quavonlimab and pembrolizumab PK samples should be collected at predose on C1D1, C2D1, C3D1, and at every 2 cycles or q6w, up to Cycle 15 then every 4 cycles or q12w thereafter. Additional PK samples should be collected at 30 minutes (+15 minutes time window) post end of infusion of MK-1308A at C1D1, C3D1, C5D1, and C7D1. Samples should also be collected at C1D8, C3D8, C4D1, C6D1, C7D8, C8D1, EOT, and 30-day Safety FU.

	Screen-ing	Treatment Period 21-Day Cycles													EOT	Posttreatment			Notes
Intervention Cycles/ Titles		1			2		3		4	5	6	7		8 to last					
Cycle Day		1	8	15	1	15	1	8	1	1	1	1	8	1	At D/C	Safety FU[a,b]	Efficacy FU[c]	Survival FU	
Scheduling Window (Days):	–28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		± 7	Q9W (± 7)	Q12W (± 7)	
Quavonlimab/ Pembro-lizumab ADA Serum Sample[d, f]		X			X		X		X	X	X	X			X	X			Quavonlimab and pembrolizumab ADA samples should be collected at predose on C1D1, C2D1, C3D1, and at every 2 cycles or q6w, up to Cycle 15 then every 4 cycles or q12w thereafter. Samples should also be collected at C4D1, C6D1, EOT and 30-day Safety FU.

ADA=antidrug antibodies; BP=blood pressure; D/C=discontinuation; EOT=End-of-Treatment; FU=follow-up; IV=intravenous; PK=pharmacokinetic; q6w =every 6 weeks; q9w=every 9 weeks; q12w=every 12 weeks; RR=respiratory rate; SpO2=peripheral oxygen saturation.

[a] If EOT visit occurs ≥30 days from last dose of study intervention, a Safety FU visit is not required. In this situation, all procedures required at both the EOT visit and the Safety FU visit should be performed.

[b] Safety FU will occur during 2 separate visits: 30 days AND 90 days after last dose. For participants continuing with imaging FU, if their 90-day Safety FU visit falls within the same window as their imaging FU visit, these visits may be combined. All procedures required at the Safety FU visit at 90 days will be performed at the imaging FU.

[c] After the primary analysis for the study: follow-up visits and tumor assessments should be performed q9w or more frequently if required by local standard of care.

[d] If ongoing PK and/or ADA sampling in Japanese participants is also deemed to be unnecessary by the Sponsor, it may be reduced or discontinued. Collection times of additional PK samples should be aligned to the time of sample collection at predose on C1D1 as possible.

[e] For participants in q6w dosing after discontinuation of lenvatinib or switching from MK-1308A to pembrolizumab, after C3D1, collect predose samples every 2 cycles up to Cycle 15 then every 4 cycles thereafter (this means for participants in q6w dosing, collect PK every time the participant comes in for IV infusions up to Cycle 15, and then every 12 weeks or every other time participants come in for their IV infusions). All predose samples should be drawn within 24 hours before infusion of MK-1308A or pembrolizumab (if MK-1308A is discontinued). Additional postdose PK samples will be drawn within 30 minutes (+15 minutes time window) after the end of MK-1308A or pembrolizumab (if MK-1308A is discontinued) infusion.

[f] For participants in q6w dosing after discontinuation of lenvatinib or switching from MK-1308A to pembrolizumab, after C3D1, collect predose samples every 2 cycles up to Cycle 15 then every 4 cycles thereafter (this means for participants in q6w dosing, collect ADA every time the participant comes in for IV infusions up to Cycle 15, and then every 12 weeks or every other time participants come in for their IV infusions). All predose samples should be drawn within 24 hours before infusion of MK-1308A or pembrolizumab (if MK-1308A is discontinued).

Section 6.5.2 Prohibited Concomitant Medications

Prophylactic use of G-CSF during the DLT observation period is not permitted.

Section 6.1 Study Intervention(s) Administered

Table 5 Study Interventions: MK-1308A or pembrolizumab used in this study are categorized as “test products” in Japan.

Table 5 Study Interventions: Lenvatinib used in this study is categorized as “product(s) used in the clinical study other than test product(s)” in Japan.

Section 6.6.3 Definition of Dose-limiting Toxicity

For safety assurance for participants, all procedures may be performed under hospitalization during the DLT assessment period.

Section 8.4.5 Pregnancy and Exposure During Breastfeeding

It is unknown whether study treatment 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. Participants who stop breastfeeding before initiation of study treatment and do not expect to resume breastfeeding will not be excluded from the study.

Accompanying documents

The clinical study conduct system in Japanese is included in the accompanying documents. The contents are as follows:

1. Clinical Study Conduct System
2. Investigators
3. Japan Enrollment Policy

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

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 to guide decisions about changes in management.

Assessment at screening and before 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 radiological disease progression by RECIST 1.1, the investigator will decide whether to continue a participant on study intervention until repeat scans 4 to 8 weeks later are obtained, as described in Section 8.2.1.6.

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 – Nontarget.

Assessment at the Confirmatory Scans

On the confirmatory scans, 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 with any prior iUPD time point
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared with 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 disease progression 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 disease progression threshold (by RECIST 1.1)

Additional scans for confirmation are to be scheduled 4 to 8 weeks from the scans on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan 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 disease progression 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 pseudoprogression, 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 Scan

If repeat scans do not confirm disease progression, and the participant continues to be clinically stable, study intervention is to continue. The regular scan schedule is to be followed. If disease progression is confirmed, participants may be discontinued from study intervention.

NOTE: If a participant has confirmed radiographic progression (iCPD) and clinically meaningful benefit, study intervention may be continued after consultation with the Sponsor. If study intervention is continued, tumor scans are to be performed after the intervals as outlined in Section 1.3.

Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (ie, after iSD/iPR/iCR), another instance of progression (another iUPD) is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the disease progression threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- 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 nontarget 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 nontarget 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 Scan above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process on the subsequent iUPD is identical to the iUPD confirmation process for the initial disease progression, with one exception, which can occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number) leading to the second iUPD. If new lesion worsening has not resolved at the confirmatory scan 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 new or worsening cause of progression indicates iCPD.

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

10.9 Appendix 9: ECOG Performance Status

As of Amendment 6, the text below is kept for historical reasons, but ECOG performance status are to be performed per standard of care.

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead
*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655 http://ecog-acrin.org/resources/ecog-performance-status	

10.10 Appendix 10: Child-Pugh Score

As of Amendment 6, the text below is kept for historical reasons, but Child-Pugh score assessments are to be performed per standard of care.

The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although it was originally used to predict mortality during surgical procedure, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation.

Scoring

The score uses 5 clinical measures of liver disease. Each measure is scored from 1 to 3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin[1] (mg/dL)	<2.0	2.0 to 3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR[2,3] Or Prothrombin time, prolongation (seconds)	<1.7 <4.0 above ULN	1.7 to 2.3 4.0-6.0 above ULN	> 2.3 >6.0 above ULN
Ascites	None	Mild (easily controlled by medication)	Moderate to Severe (poorly controlled)
Hepatic encephalopathy[4]	None	Grade I-II (mild or moderate)	Grade III-IV (severe or coma)

1 In primary sclerosing cholangitis and primary biliary cirrhosis, the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/L (4 mg/dL) and the upper limit for 2 points is 170 µmol/L (10 mg/dL).

2 Different textbooks and publications use different measures. Some older reference works substitute PT prolongation for INR

3 For patients on anticoagulants (eg, Coumadin), only 1 point is assigned irrespective of the patient's INR and PT value.

4 Hepatic encephalopathy graded according to West Haven Criteria for Semi-quantitative Grading of Mental Status: Adapted from: Conn H, Lieberthal M. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins; 1979.

- Grade I: Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- Grade II: Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior
- Grade III: Somnolence to semi-stupor, but responsive to verbal stimuli
  Confusion; Gross disorientation
- Grade IV: Coma (unresponsive to verbal or noxious stimuli)

Interpretation

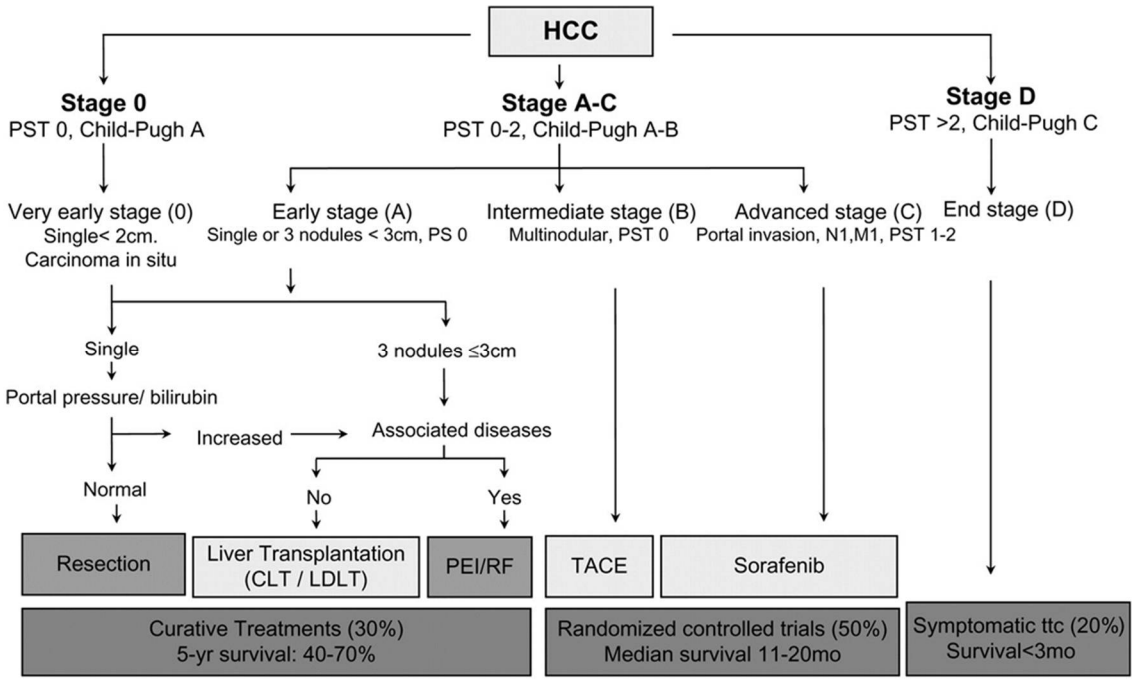
Chronic liver disease is classified into Child-Pugh class A to C, using the added score from above.

Points	Class	One-year Survival	Two-year Survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

10.11 Appendix 11: Barcelona Clinic Liver Cancer Staging System

The Barcelona Clinic Liver Cancer staging system is shown in Figure 3 below [Llovet, J. M., et al 2008].

Figure 3 Barcelona Clinic Liver Cancer Staging System



CLT=cadaveric liver transplantation; HCC=hepatocellular carcinoma; LDLT=living donor liver transplantation; PEI=percutaneous ethanol injection; PST=performance status test; RF=radio frequency (ablation); TACE=transarterial chemoembolization.

10.12 Appendix 12: NYHA Criteria

As of Amendment 6, the text below is kept for historical reasons, but NYHA criteria assessments are to be performed per standard of care.

The NYHA Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac participants. Based on 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].	

10.13 Appendix 13: American Association for the Study of Liver Diseases (AASLD) Liver Imaging Reporting and Data System (LI-RADS) 5 Criteria

AASLD LI-RADS 5 Criteria for radiographic diagnosis of hepatocellular carcinoma using CT/MRI are shown in Table 23. Cirrhosis is required for radiographic diagnosis.

Table 23 AASLD LI-RADS 5 Criteria

Size	Criteria	Comments
≥20 mm	APHE (nonrim) **AND** one or more of following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth	Equivalent to OPTN 5B or 5X
10-19 m	APHE (nonrim) **AND** the following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth	Equivalent to OPTN 5A
	APHE (nonrim) **AND** "Washout" (nonperipheral)	Equivalent to 2010 AASLD criteria
	APHE (nonrim) **AND** threshold growth	Equivalent to OPTN 5A-5G

Threshold growth = size increase of a mass by ≥ 50% in ≤ 6 months; "Washout" = washout appearance; "Capsule" = capsule appearance.
Abbreviation: APHE, arterial phase hyperenhancement.

Table source: [Marrero, J. A., et al 2018]

10.14 Appendix 14: Abbreviations

Abbreviation	Expanded Term
AASLD	American Association for the Study of Liver Diseases
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AFP	alpha fetoprotein
ALT	alanine aminotransferase
Anti-HBc	antihepatitis B core antibody, Total
Anti-HBs	antihepatitis B surface antibody
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
BCLC	Barcelona Clinic Liver Cancer
BICR	blinded independent central review
BMI	body mass index
BOR	best overall response
BP	blood pressure
BSC	best supportive care
BW	body weight
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CP	Child-Pugh
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE v5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
D	deescalate to the next lower dose
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee

DNA	deoxyribonucleic acid
DOR	duration of response
DU	current dose is unacceptably toxic
E	escalate to the next higher dose
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group performance status
EDC	electronic data collection
eDMC	external Data Monitoring Committee
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End-of-Treatment
EU CTR	European Union Clinical Trial Regulations
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin-embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FSH	follicle stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HECI	hepatic events of clinical interest
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HUVEC	human umbilical vein endothelial cell
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements

iCRO	imaging CRO
iCPD	iRECIST confirmed progressive disease
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgM	immunoglobulin M
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IMP	investigational medicinal product
ICMJE	International Committee of Medical Journal Editors
INR	international normalized ratio
IO	Immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITT	intention-to-treat
IUD	intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
kg	kilogram
LAM	lactational amenorrhea method
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
MUGA	multigated acquisition scan
NCI	National Cancer Institute
NCT	National Clinical Trial
NSCLC	non-small-cell lung cancer
NYHA	New York Heart Association
ONJ	osteonecrosis of the jaw
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease

PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
Pgp	P-glycoprotein
PI	Product Information
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
q2w	every 2 weeks
q3w	every 3 weeks
q6w	every 6 weeks
q9w	every 9 weeks
q12w	every 12 weeks
qd	once daily
QoD	every other day
QoL	quality of life
RBC	red blood cells
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RET	ret proto-oncogene
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	respiratory rate
RTK	receptor tyrosine kinase
S	stay at the current dose
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SD	stable disease
SIM	Site Imaging Manual
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SpO2	peripheral oxygen saturation
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TACE	transarterial chemoembolization
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTD	time to deterioration
TTP	time to progression

ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VS	vital sign
WBC	white blood cell
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

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