Official Protocol Title:	A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) with Pembrolizumab (MK-3475) in Combination with Transarterial Chemoembolization (TACE) Versus TACE in Participants with Incurable/Non-metastatic Hepatocellular Carcinoma (LEAP-012)
NCT Number:	NCT04246177
Document Date:	08-Jul-2025

Title Page

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Protocol Title: A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) with Pembrolizumab (MK-3475) in Combination with Transarterial Chemoembolization (TACE) Versus TACE in Participants with Incurable/Non-metastatic Hepatocellular Carcinoma (LEAP-012)

Protocol Number: 012-06 (E7080-G000-318)

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

Sponsor Name:

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

The study is co-funded by MSD and Eisai.

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

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Approval Date: 08 July 2025

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 06	08-JUL-2025	The primary reason for this amendment is to update study conduct and procedures after the last inferential analysis for the study.
Amendment 05	28-NOV-2022	This amendment has been generated to reduce the sample size from 950 to 450 participants and subsequently update the statistical analysis plan. CCI [redacted] Additionally, the frequency of study visits is extended from Q3W (21-day cycles) to Q6W (42-day cycles) after the first 3 months of therapy.
Amendment 04	20-AUG-2021	CCI [redacted]
Amendment 03	28-MAY-2021	This amendment has been generated to address changes to HBV inclusion criteria, add further clarification regarding acceptable prior locoregional therapy (defined in the exclusion criteria), dose modification changes for pembrolizumab, and applicable changes to comply with the lenvatinib and pembrolizumab label updates.
Amendment 02	02-JUL-2020	To CCI [redacted], add MK-7902 program-level updates, and clarify or change study procedures.
Amendment 01	19-DEC-2019	To correct a pagination error.
Original Protocol	16-DEC-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendment:

The primary reason for this amendment is to update study conduct and procedures after the last inferential analysis for the study.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.3, Schedule of Activities	Added text to summarize information regarding procedures/assessments for participants who have discontinued study treatment or are receiving placebo after the last inferential analysis.	This change was made to update study conduct and procedures after the last inferential analysis for the study.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1, Synopsis Section 4.1, Overall Design Section 4.4, Beginning and End of Study Definition Section 7.2, Participant Withdrawal From the Study	Added text to describe participant discontinuation and simplification of procedures following the last inferential analysis for the study.	To discontinue participants not receiving lenvatinib therapy and simplify study procedures for participants on lenvatinib therapy following the last inferential analysis for the study.
Section 1.1, Synopsis Section 4.1, Overall Design Section 4.4, Beginning and End of Study Definition	Added text related to extension study enrollment.	To allow participants who are on lenvatinib therapy to rollover to an extension study.
Section 1.2, Schema	Footnotes: Added note refers to Section 1.3 for posttreatment follow-up information for participants who have discontinued study treatment or are receiving placebo.	To specify required follow-up procedures.
Section 2.1, Study Rationale	Added 95% CI for the KEYNOTE-240 HR data presented.	To clarify that the data presented are 95% confidence intervals.

Section Number and Name	Description of Change	Brief Rationale
Section 9.10, Subgroup Analyses	Removed TACE type and TACE imaging from subgroup analysis.	TACE type and TACE imaging were in part determined after randomization and are not appropriate for subgroup analysis. TACE type and TACE imaging are not considered as baseline characteristics. This change is made to align with supplemental SAP.
	Removed subgroup analysis of ORR.	ORR is not under multiplicity control and is not required for subgroup analysis.
Throughout the document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

Table of Contents

DOCUMENT HISTORY **3**
PROTOCOL AMENDMENT SUMMARY OF CHANGES **4**
1 PROTOCOL SUMMARY **15**
1.1 Synopsis **15**
1.2 Schema **20**
1.3 Schedule of Activities **21**
2 INTRODUCTION **34**
2.1 Study Rationale **34**
2.2 Background **35**
2.2.1 Pharmaceutical and Therapeutic Background 35
2.2.1.1 Lenvatinib 35
2.2.1.2 Pembrolizumab 36
2.2.1.3 Hepatocellular Carcinoma: Epidemiology and Current Therapeutic Options 37
2.2.1.4 Immunotherapy Interventions in HCC 38
2.2.1.5 Clinical Data on Lenvatinib, Pembrolizumab, and TACE as Single Agents for the Treatment of HCC 39
2.2.1.6 Scientific Rationale for the Combination of Lenvatinib, Pembrolizumab, and TACE 41
2.2.1.7 Clinical Data on Lenvatinib in Combination With Pembrolizumab for Treatment of Solid Tumors and HCC 41
2.2.2 Preclinical and Clinical Studies 42
2.2.3 Ongoing Clinical Studies 42
2.3 Benefit/Risk Assessment **42**
3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS **42**
4 STUDY DESIGN **45**
4.1 Overall Design **45**
4.2 Scientific Rationale for Study Design **47**
4.2.1 Rationale for Stratification Factors 47
4.2.2 Rationale for Endpoints 48
4.2.2.1 Efficacy Endpoints 48
4.2.2.1.1 RECIST 1.1 48
4.2.2.1.2 mRECIST 49
4.2.2.2 Safety Endpoints 49
4.2.2.3 Patient-reported Outcomes 49
4.2.2.3.1 EORTC QLQ-C30 49

4.2.2.3.2 EORTC QLQ-HCC18 49
4.2.2.3.3 EQ-5D-5L 49
4.2.2.4 Pharmacokinetic Endpoints 50
4.2.2.5 Pharmacodynamic Endpoints 50
4.2.2.6 Planned Exploratory Biomarker Research 50
4.2.3 Rationale for the Use of Comparator/Placebo 52
4.3 Justification for Dose 52
4.3.1 Pembrolizumab 52
4.3.2 Lenvatinib 53
4.3.3 Maximum Dose/Exposure for This Study 54
4.4 Beginning and End of Study Definition 54
4.4.1 Clinical Criteria for Early Study Termination 54
5 STUDY POPULATION 55
5.1 Inclusion Criteria 55
5.2 Exclusion Criteria 59
5.3 Lifestyle Considerations 62
5.3.1 Meals and Dietary Restrictions 62
5.3.2 Contraception 63
5.4 Screen Failures 63
5.5 Participant Replacement Strategy 63
6 STUDY INTERVENTION 63
6.1 Study Intervention(s) Administered 63
6.2 Preparation/Handling/Storage/Accountability 65
6.2.1 Dose Preparation 65
6.2.2 Handling, Storage, and Accountability 65
6.3 Measures to Minimize Bias: Randomization and Blinding 66
6.3.1 Intervention Assignment 66
6.3.2 Stratification 66
6.3.3 Blinding 67
6.4 Study Intervention Compliance 67
6.5 Concomitant Therapy 67
6.5.1 Allowed Concomitant Medications 67
6.5.2 Prohibited Concomitant Medications 68
6.5.3 Drug-Drug Interaction 69
6.5.4 Rescue Medications and Supportive Care 70
6.6 Dose Modification (Escalation/Titration/Other) 70
6.6.1 Lenvatinib Dose Modification 70
6.6.1.1 Management of Hypertension 72

6.6.1.2 Management of Proteinuria....74
6.6.1.3 Management of Diarrhea....75
6.6.1.4 Management of Thromboembolic Events....75
6.6.1.5 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome....76
6.6.1.6 Management of Hypocalcemia....76
6.6.1.7 Management of Hemorrhage....76
6.6.1.8 Management of Gastrointestinal Perforation or Fistula Formation....76
6.6.2 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)....77
6.6.2.1 Dose Modification and Toxicity Management for Nonhepatic Immune-related AEs Associated with Pembrolizumab....77
6.6.3 Guidance for Management of Hepatic Events of Clinical Interest....85
6.6.3.1 Management of HECI for Lenvatinib Toxicity:....86
6.6.3.2 Management of HECI for Pembrolizumab/ IV Placebo....87
6.6.4 Dose Modifications for Overlapping Toxicities....88
6.6.5 Other Allowed Dose Interruptions....89
6.6.6 Second Course....90
6.7 Intervention After the End of the Study....90
6.8 Clinical Supplies Disclosure....90
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL....90
7.1 Discontinuation of Study Intervention....90
7.2 Participant Withdrawal From the Study....91
7.3 Lost to Follow-up....92
8 STUDY ASSESSMENTS AND PROCEDURES....92
8.1 Administrative and General Procedures....93
8.1.1 Informed Consent....93
8.1.1.1 General Informed Consent....93
8.1.2 Inclusion/Exclusion Criteria....94
8.1.3 Participant Identification Card....94
8.1.4 Medical History....94
8.1.5 Prior and Concomitant Medications Review....94
8.1.5.1 Prior Medications....94
8.1.5.2 Concomitant Medications....94
8.1.6 Assignment of Screening Number....94
8.1.7 Assignment of Treatment/Randomization Number....95
8.1.8 Study Intervention Administration....95

8.1.8.1 Timing of Dose Administration 95
8.1.8.1.1 TACE 95
8.1.8.1.2 Lenvatinib/Oral Placebo 96
8.1.8.1.3 Pembrolizumab/IV Placebo 96
8.1.9 Discontinuation and Withdrawal 96
8.1.10 Participant Blinding/Unblinding 96
8.1.11 Calibration of Equipment 97
8.2 Efficacy/Immunogenicity Assessments 97
8.2.1 Tumor Imaging and Assessment of Disease 97
8.2.1.1 Initial Tumor Imaging 98
8.2.1.2 Tumor Imaging During the Study 98
8.2.1.3 End-of-Treatment and Follow-up Tumor Imaging 99
8.2.1.4 RECIST 1.1 Assessment of Disease 99
8.2.1.5 Modified RECIST Assessment of Disease 99
8.2.2 Patient-reported Outcomes 100
8.3 Safety Assessments 100
8.3.1 Physical Examinations 100
8.3.1.1 Full Physical Examination 101
8.3.1.2 Directed Physical Examination 101
8.3.2 Vital Signs 101
8.3.3 Electrocardiograms 101
8.3.4 Echocardiogram or Multiple Gated Acquisition Scan 102
8.3.5 Child-Pugh Score 102
8.3.6 Clinical Safety Laboratory Assessments 102
8.3.6.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis) 103
8.3.6.2 Pregnancy Test 103
8.3.7 Performance Assessments 104
8.3.7.1 Eastern Cooperative Oncology Group Performance Scale 104
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events 104
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 104
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events 107
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information 107
8.4.4 Regulatory Reporting Requirements for SAE 107
8.4.5 Pregnancy and Exposure During Breastfeeding 107
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs 108

8.4.7 Events of Clinical Interest....108
8.5 Treatment of Overdose....109
8.5.1 Reporting of Overdose....109
8.6 Pharmacokinetics....109
8.7 Pharmacodynamics....110
8.8 Biomarkers....110
8.8.1 Planned Genetic Analysis Sample Collection....110
8.9 Medical Resource Utilization and Health Economics....110
8.10 Visit Requirements....111
8.10.1 Screening....111
8.10.2 Treatment Period....112
8.10.3 Posttreatment Visits....112
8.10.3.1 Safety Follow-up Visits....112
8.10.3.2 Efficacy Follow-up Visits....112
8.10.3.3 Survival Follow-up....112
8.10.4 Survival Status....113
9 STATISTICAL ANALYSIS PLAN....113
9.1 Statistical Analysis Plan Summary....113
9.2 Responsibility for Analyses/In-house Blinding....116
9.3 Hypotheses/Estimation....116
9.4 Analysis Endpoints....116
9.4.1 Efficacy Endpoints....116
9.4.2 Safety Endpoints....117
9.5 Analysis Populations....117
9.5.1 Efficacy Analysis Populations....117
9.5.2 Safety Analysis Populations....117
9.5.3 PRO Analysis Populations....118
9.6 Statistical Methods....118
9.6.1 Statistical Methods for Efficacy Analyses....118
9.6.1.1 Progression-free Survival....118
9.6.1.2 Overall Survival....120
9.6.1.3 Objective Response....121
9.6.1.4 Disease Control....121
9.6.1.5 Time to Progression....121
9.6.1.6 Duration of Response....122
9.6.1.7 Analysis Strategy for Key Efficacy Variables....123
9.6.2 Statistical Methods for Safety Analyses....124
9.6.2.1 Overall Safety Assessment....124

9.6.2.2 Assessment of Safety Topics of Special Interest 126
9.6.3 Statistical Methods for PRO Analyses 126
9.6.4 Summaries of Baseline Characteristics and Demographics 126
9.7 Interim Analyses 126
9.7.1 Safety Interim Analyses 127
9.7.2 Efficacy Interim Analyses 127
9.8 Multiplicity 128
9.8.1 Progression-free Survival 129
9.8.2 Overall Survival 129
9.8.3 Safety Analyses 131
9.9 Sample Size and Power Calculations 131
9.9.1 Sample Size and Power for Efficacy Analyses 131
9.10 Subgroup Analyses 132
9.11 Compliance (Medication Adherence) 132
9.12 Extent of Exposure 132
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 133
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 133
10.1.1 Code of Conduct for Clinical Trials 133
10.1.2 Financial Disclosure 135
10.1.3 Data Protection 136
10.1.3.1 Confidentiality of Data 136
10.1.3.2 Confidentiality of Participant Records 136
10.1.3.3 Confidentiality of IRB/IEC Information 136
10.1.4 Committees Structure 137
10.1.4.1 Scientific Advisory Committee (SAC) 137
10.1.4.2 Executive Oversight Committee 137
10.1.4.3 External Data Monitoring Committee 137
10.1.5 Publication Policy 137
10.1.6 Compliance with Study Registration and Results Posting Requirements 138
10.1.7 Compliance with Law, Audit, and Debarment 138
10.1.8 Data Quality Assurance 139
10.1.9 Source Documents 139
10.1.10 Study and Site Closure 140
10.2 Appendix 2: Clinical Laboratory Tests 141
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 144
10.3.1 Definitions of Medication Error, Misuse, and Abuse 144

10.3.2 Definition of AE 144
10.3.3 Definition of SAE 145
10.3.4 Additional Events Reported 147
10.3.5 Recording AE and SAE 147
10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor 151
10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation 153
10.5 Appendix 5: Contraceptive Guidance 154
10.5.1 Definitions 154
10.5.2 Contraception Requirements 155
10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research 156
10.7 Appendix 7: Country-specific Requirements 157
10.7.1 Germany 157
10.7.2 United Kingdom 158
10.7.3 Portugal 159
10.7.4 South Korea 159
10.7.5 Ireland 161
10.7.6 Japan 161
10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression 162
10.9 Appendix 9: ECOG Performance Status 163
10.10 Appendix 10: Child-Pugh Score 164
10.11 Appendix 11: Barcelona Clinic Liver Cancer Staging System 166
10.12 Appendix 12: NYHA Criteria 167
10.13 Appendix 13: American Association for the Study of Liver Diseases (AASLD) Liver Imaging Reporting and Data System (LI-RADS) 5 Criteria 168
10.14 Appendix 14: Hepatoma Arterial-embolization Prognostic (HAP) Score 169
10.15 Appendix 15: ALBI Grade Nomogram 170
10.16 Appendix 16: Abbreviations 171
11 REFERENCES 176

LIST OF TABLES

Table 1 Study Schedule of Activities....22
Table 2 Adequate Organ Function Laboratory Values....59
Table 3 Study Interventions....64
Table 4 Dose Modification for Lenvatinib Treatment-Related Toxicity....71
Table 5 Dose Modification Guidelines for Lenvatinib-related Adverse Events (for the Lenvatinib-Pembrolizumab Combination)....72
Table 6 Dose Modification and Toxicity Management Guidelines for Nonhepatic Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations....78
Table 7 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines....83
Table 8 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events....106
CCI [redacted]
Table 12 Analysis Strategy for Key Efficacy Endpoints....124
Table 13 Analysis Strategy for Safety Parameters....125
Table 14 Summary of Interim and Final Analyses Strategy....128
Table 15 Efficacy Boundaries and Properties for Progression-free Survival Analysis....129
Table 16 Efficacy Boundaries and Properties for Overall Survival Analyses....130
Table 17 Protocol-required Safety Laboratory Assessments....142
Table 18 AASLD LI-RADS 5 Criteria....168

LIST OF FIGURES

Figure 1 Study Diagram 20
CCI [redacted]
Figure 3 Barcelona Clinic Liver Cancer Staging System.....166

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) with Pembrolizumab (MK-3475) in Combination with Transarterial Chemoembolization (TACE) Versus TACE in Participants with Incurable/Non-metastatic Hepatocellular Carcinoma (LEAP-012)

Short Title: Phase 3 Study of Pembrolizumab and Lenvatinib in Combination with TACE for Incurable/Non-metastatic Hepatocellular Carcinoma

Acronym: LEAP-012

Hypotheses, Objectives, and Endpoints:

Although traditional Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) references a maximum of 5 target lesions in total and 2 per organ, throughout this protocol the term RECIST 1.1 refers to an adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additionally, new intrahepatic lesions must meet Liver Imaging Reporting and Data System version 5 (LI-RADS 5) criteria (Appendix 13) to be considered unequivocal as per RECIST 1.1. Refer to Section 4.2.2.1 for further details.

In 1L therapy of participants with incurable/nonmetastatic hepatocellular carcinoma (HCC):

Primary Objectives	Primary Endpoints
- Objective: To compare pembrolizumab plus lenvatinib in combination with TACE vs. placebo plus TACE with regard to progression-free survival (PFS) per RECIST 1.1 assessed by blinded, independent central review (BICR) - Hypothesis (H1): Pembrolizumab plus lenvatinib in combination with TACE is superior to placebo plus TACE with respect to PFS per RECIST 1.1 assessed by BICR.	- PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

- Objective: To compare pembrolizumab plus lenvatinib in combination with TACE vs. placebo plus TACE with regard to overall survival (OS). - Hypothesis (H2): Pembrolizumab plus lenvatinib in combination with TACE is superior to placebo plus TACE with respect to OS.	- OS: the time from randomization to death due to any cause
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate pembrolizumab plus lenvatinib in combination with TACE vs. placebo plus TACE with regard to PFS, objective response rate (ORR), disease control rate (DCR), duration of response (DOR) and time to progression (TTP) per mRECIST assessed by BICR.	- PFS - OR: CR or PR. - Disease control (DC): a best overall response of complete response (CR), partial response (PR), or stable disease (SD). - DOR: the time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first. - TTP: the time from randomization to the first documented disease progression
- Objective: To evaluate the safety and tolerability of pembrolizumab plus lenvatinib in combination with TACE versus placebo plus TACE.	- Adverse Events (AEs), serious adverse events (SAEs), and hepatic AEs - Study intervention discontinuations due to AEs
- Objective: To evaluate pembrolizumab plus lenvatinib in combination with TACE versus placebo plus TACE with regard to efficacy outcomes per RECIST 1.1 assessed by BICR.	- OR, DC, DOR, and TTP

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	The treatment of participants with incurable/nonmetastatic hepatocellular carcinoma
Population	Participants with incurable/nonmetastatic hepatocellular carcinoma
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Investigator Participants or Subjects Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 8 years, from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 450 participants will be randomized 1:1 to 1 of 2 treatment arms.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Arm A	Pembro-lizumab	400 mg	Q6W	IV infusion	Day 1 of cycle Q6W for 2 years	Test Product
	Lenva-tinib	12 mg (BW ≥60 kg) or 8 mg (BW <60 kg)[a]	Once daily	Oral	Daily[a,b] for up to 2 years	Test Product
	TACE	Variable	No more than once a month.	Intra-arterial	Up to 2 treatments/ lesion, maximum 4 treatments	Back-ground Treatment
Arm B	IV Placebo	0 mg, 0.90% w/v NaCl	Q6W	IV infusion	Day 1 of cycle Q6W for 2 years	Placebo
	Oral Placebo	N/A	Once daily	Oral	Daily[a,b] for up to 2 years	Placebo
	TACE	Variable	No more than once a month.	Intra-arterial	Up to 2 treatments/ lesion, maximum 4 treatments	Back-ground Treatment

BW = body weight; IV = intravenous; N/A = not applicable; Q6W = every 6 weeks; w/v = weight/volume; TACE = transarterial chemoembolization.
a. Lenvatinib dosing is based on actual body weight at screening and will be fixed for the duration of the study.
b. Hold lenvatinib/oral placebo 2 days pre- and at least 7 days post-TACE

Other current or former name(s) or alias(es) for study intervention(s) are as follows: lenvatinib: E7080, MK-7902, LENVIMA®, KISPLYX®; pembrolizumab: MK-3475, KEYTRUDA®

Total Number

2 Arms

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 and verified by blinded independent central review per RECIST 1.1, unacceptable AE(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. This protocol does not allow participants to cross over to the other arm if they experience progression.

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 study intervention for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 and verified by BICR, the start of a new anti-cancer treatment, withdrawal of consent, pregnancy, death, or loss to follow-up, whichever occurs first. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. Following the last inferential analysis for the study, participants who discontinued study treatment or are receiving placebo will be discontinued from the study. Participants who are on lenvatinib therapy may be enrolled in an extension study.

Study Governance Committees:

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

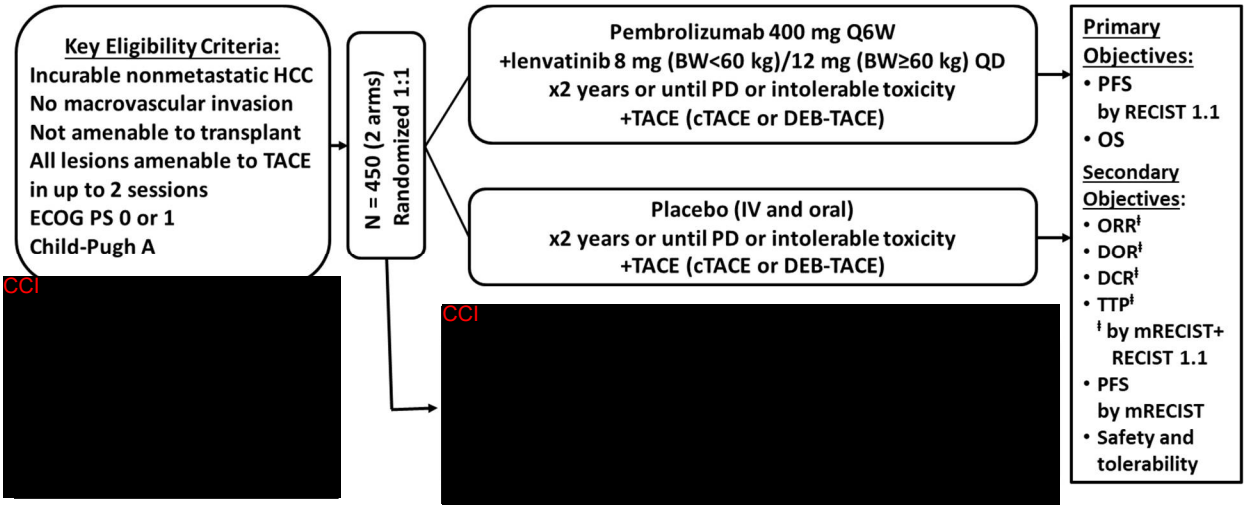
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 16.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram



AFP = alpha fetoprotein; ALBI = albumin-bilirubin; BW = body weight; cTACE = conventional transarterial chemoembolization; DCR = disease control rate; DEB-TACE = drug-eluting beads- transarterial chemoembolization; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; HCC = hepatocellular carcinoma; IV = intravenous; mRECIST = modified Response Evaluation Criteria in Solid Tumors; ORR = objective response rate; PD = progressive disease; OS = overall survival; PFS = progression-free survival; Q6W = every 6 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; TACE = transarterial chemoembolization; TTP = time to progression.

[a] Tumor burden, utilizing the 6 and 12 rule; 3 categories: ≤6 versus >6 but ≤12 versus >12
Tumor burden = (largest tumor size in cm) + (number of tumors).

Note: Refer to Section 1.3 for posttreatment follow-up information for participants who have discontinued study treatment or are receiving placebo.

1.3 Schedule of Activities

Following the last inferential analysis for the study, all participants who discontinued study treatment or are receiving placebo will be discontinued from study. Additionally, participants on lenvatinib therapy may be enrolled in an extension study.

The following procedures/assessments are not required following the last inferential analysis for the study:

- PK sample collection
- ADA/Biomarker sample collection
- ePRO assessments
- Follow-up for subsequent antineoplastic therapy status, and survival

The following procedures/assessments are to occur per standard of care following the last inferential analysis for the study:

- Clinical laboratory tests
- Imaging (not to be submitted to BICR)

Table 1 Study Schedule of Activities

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Administrative and General Procedures														
Informed consent	X													
Inclusion/ exclusion	X													Refer to Appendix 7 for country-specific criteria.
Participant ID card	X	X												Update ID card at randomization visit with randomization number.
Demographics	X													
Medical/surgical history	X													Including alcohol and smoking history.
Prior/ concomitant medication review	X	X	X	X	X	X	X	X	X	X	X			Record concomitant meds for 90 days after last dose, or for up to 120 days after last dose for SAEs.
Randomization and study intervention assignment via IRT		X												Participants will be randomized on C1D1 after confirmation of eligibility. All procedures and assessments on C1D1 should be performed after randomization.

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Subsequent antineoplastic treatment status											X	X	X	All antineoplastic therapy will be recorded until time of death or termination of survival follow-up. If a clinic visit is not feasible, follow-up information may be obtained via other means of contact (eg, telephone, video call, mail, or email).
Survival status		←----------							----------→					On Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Schedule of Study Intervention														
Lenvatinib or oral placebo dispensing		X			X		X	X	X					
Lenvatinib or oral placebo administration		X	X	X	X	X	X	X	X					Lenvatinib 12 mg (BW≥60 kg) or 8 mg (BW<60 kg) (Arm A) orally or oral placebo (Arm B) QD until PD or intolerable toxicity. Hold lenvatinib/oral placebo 2 days pre- and at least 7 days post-TACE. A follow-up visit is required before resuming lenvatinib after each TACE procedure to ensure resolution of postembolization syndrome.

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Pembrolizumab or IV placebo administration		X					X		X					Pembrolizumab 400 mg IV Q6W (Arm A) or normal saline placebo IV Q6W (Arm B) for 2 years (approximately 17 doses).
TACE				◄———	———	———	———	———	———►					First TACE C1D14 - C2D7. CCI [redacted]

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Efficacy Procedures														
Tumor assessment – chest, abdomen, and pelvis (CT/MRI)	X	<---------->								X		X		Historical scans performed within 28 days prior to randomization but before documented informed consent may be used if consistent with protocol requirements per BICR. All imaging assessments should follow calendar days and not be adjusted for cycle delays. The first on study imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated until discontinuation of study intervention. For participants continuing with imaging FU at ≥9W, 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 at ≥9W.

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Clinical Procedures or Assessments														
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X		AEs: monitored up to 90 days after last dose or 30 days after the last dose if the participant initiates new anticancer therapy. SAEs: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new antineoplastic therapy, whichever is sooner. In the case of hepatic ECIs, additional tests to be performed by a central laboratory, if possible.
Full physical examination	X										X			To be performed within 7 days prior to start of study intervention.
Directed physical examination		X	X	X	X	X	X	X	X	X				
Child-Pugh Score	X				X		X	X	X					Within 7 days prior to start of study intervention.
Vital signs (resting BP, pulse, RR, and temp) and weight	X	X	X	X	X	X	X	X	X	X	X			

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Height	X													
NYHA Cardiac Disease Classification	X													.
HAP score	X													
12-lead ECG	X	X					X		X (C6D1, and Day 1 of every second cycle after)	X	X			For high-risk participants (Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib/oral placebo is discontinued, ECGs are only required at the EOI and Safety Follow-up Visits.
MUGA or ECHO for LVEF assessment	X										X			Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study.
Gastro-enterological upper endoscopy	X													Gastroenterological upper endoscopy must be performed within 3 months prior to randomization.
ECOG performance status	X	X			X		X	X	X		X			To be assessed within 7 days prior to starting study intervention. Should be assessed prior to dosing on D1 of each cycle.

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Local Laboratory Procedures and Assessments														Clinical laboratory assessments may be conducted any time within 72 hours prior to the scheduled visit, unless otherwise specified. Procedures/assessments should be performed prior to administration of study intervention.
Pregnancy test (WOCBP only)	X				X		X	X	X	X	X	X		WOCBP require a negative test prior to randomization and within 24 hours for urine or 72 hours for serum prior to the first dose of study intervention. If less than 24 hours have elapsed between this pregnancy test and the first dose of study intervention, another pregnancy test is not required.
PT/INR	X				X		X	X	X	X	X			To be assessed within 7 days prior to first dose of study intervention.
CBC with differential	X			X	X	X	X	X	X	X	X			To be assessed within 7 days prior to first dose of study intervention.
Clinical chemistry laboratory assessments	X			X	X	X	X	X	X	X	X			To be assessed within 7 days prior to first dose of study intervention. Every effort should be made to collect samples at the same time of day.

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Urine dipstick testing	X			X	X	X	X	X	X	X				Performed locally within 7 days prior to start of intervention. Participants may return for testing if monitoring is required as follows: requires 24-hour urine protein analysis if new proteinuria (dipstick ≥2+) is detected on urinalysis; repeat testing for participants with proteinuria ≥2+ should be performed until the results have been 1+ or negative for 2 consecutive treatment cycles.
T3/FT3, FT4, and TSH	X				X			X	X	X				After C1, participant may be dosed even if thyroid evaluations are not available prior to dosing; however, the results must be available and reviewed before the next scheduled visit. FT3 is acceptable where T3 cannot be determined.
AFP	X							X	X (C6, and every 2 cycles after that)	X	X			A visit window of ±7 days will apply.

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
HIV	X													Testing is not required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
Central/Local Laboratory Assessments														
Anti-HCV (IgG)	X													
<u>If Anti-HCV (IgG) positive:</u>														If these conditions are met, the following test will be performed within 28 days prior to study intervention.
• HCV genotype	X													Participant may be randomized if results are pending, and participant meets all other eligibility criteria.
• HCV viral load	X													
Anti-HBc (total and IgM), anti-HBs, HBV viral load, HBsAg	X													

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
PK/Pharmacodynamic/Biomarker Assessment														
Pembrolizumab PK blood sample		X					X							Collect predose of 2nd pembrolizumab/placebo administration, regardless of cycle, only if TACE was performed in between.
Pembrolizumab ADA		X					X							Collect predose of 2nd pembrolizumab/placebo administration, regardless of cycle, only if TACE was performed in between.
CCI [redacted]		X												Collect predose.
[redacted]		X			X		X	X	X	X				Collect at predose on C1D1, C2D1, C3D1, C4D1, C6D1, and Q6W thereafter. Also, collect at the EOI visit.
[redacted]		X			X		X		X (C5)	X				Collect predose on C1D1, C2D1, C3D1, C5D1, and at EOI visit.
[redacted]		X			X		X	X	X	X				Collect predose on C1D1, C2D1, C3D1, C4D1, C6D1, and Q6W thereafter. Collect also at the EOI visit.

Study Period	**Screening**	**Study Intervention Period**								**EOI**	**Poststudy Intervention**			**Notes**
		21-Day Cycles							**42-Day Cycles**					
Intervention Cycles		**1**			**2**		**3**	4[a]	**5+-**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU**	**Survival FU**	**Frequency of the cycles will be Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond.[a] Please refer to Appendix 7 for country-specific requirements.**
Scheduling Window (Days):	**–28 to –1, unless otherwise specified**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C[b]**	**30 Days[b] and 90 Days After Last Dose (+ 7)**	**Q9W (± 7)**	**Q12W (± 7)**	
Newly obtained or archival tumor tissue collection (optional)	X													Tissue is not required for enrollment, however submission of archival tissue is strongly encouraged, if available. Formalin-fixed, paraffin-embedded block specimens are preferred to slides.
Patient-Reported Outcomes														
ePROs in the following order: EORTC QLQ-C30, EORTC QLQ-HCC18, EQ-5D-5L		X					X		X	X	X			Administer ePROs prior to AE evaluation, disease status notification, and dosing. ePROs are to be performed at least up to 2 years or EOT, whichever occurs first, at discontinuation, and at the 30-day posttreatment discontinuation follow-up visit. A visit window of ±7 days will apply.

ADA = antidrug antibody(ies); AE = adverse event; AFP = alpha fetoprotein; Anti-HBc = antihepatitis B core antibody, total; Anti-HBs = antihepatitis B surface antibody; BP = blood pressure; BW = body weight; C1D1 = Cycle 1 Day 1; CBC = complete blood count; CT = computed tomography; CX = Cycle X; D/C = discontinuation; DX = Day X, ECG = electrocardiogram; ECHO = echocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOI = End of Intervention; EORTC QLQ= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of trial; ePRO = electronic patient-reported outcome; EQ-5D-5L = European Quality of Life 5-dimension, 5-level Questionnaire; FT3 = free triiodothyronine; FT4 = free thyroxine; FU = follow-up; HAP = Hepatoma arterial-embolization prognostic score; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = hour; ID = identification; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; IRT = interactive response technology; IV = intravenous; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PD = progressive disease; NYHA = New York Heart Association; PK = pharmacokinetic; PT = prothrombin time; Q3W = every 3 weeks; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QD = once daily; RNA = ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; T3 = triiodothyronine; TACE = transarterial chemoembolization; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

[a] If pembrolizumab/placebo is administered on Cycle 4 Day 1, then Cycle 5 Day 1 should occur 6 weeks after, and all subsequent cycles should be Q6W. If pembrolizumab/placebo is not administered on Cycle 4 Day 1, then Cycle 5 Day 1 should occur 3 weeks after, and all subsequent cycles should be Q6W.

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

2 INTRODUCTION

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 incurable, nonmetastatic HCC represent a group with high unmet need, low survival rates, and few effective therapeutic options. Subsequently, although it is estimated that only 30% of HCC patients are eligible for TACE, a recent large global study (n=1630, OPTIMIS) showed that 44% of patients who receive TACE do not meet international guidelines for TACE [Peck-Radosavljevic, M. 2018].

Locoregional therapy, primarily with TACE, is the recommended treatment modality for patients with intermediate stage HCC, defined as those whose tumors are confined to the liver without vascular invasion, but not amenable to curative therapy with resection or thermal ablation [Marrero, J. A., et al 2018] [Omata, M., et al 2017] [Vogel, A., et al 2018]. Previous studies evaluating the combination of TKIs, including sorafenib, brivanib and orantinib with TACE did not show improvement on patient outcomes [Lencioni, R., et al 2016] [Meyer, T., et al 2017] [Kudo, M., et al 2014] [Kudo, M., et al 2018]. Subsequently, TACE remains the mainstay of treatment for the intermediate HCC patient population worldwide, as newer options, such as TARE, are significantly more expensive and lack clinical data to show superiority over TACE. Patients who progress after TACE are then considered to have advanced HCC and typically placed on systemic therapy.

Lenvatinib (also known as E7080 or MK-7902; hereafter called lenvatinib) is now approved for the 1L treatment of advanced HCC in many parts of the world. In a randomized, open-label, Phase 3 study (REFLECT), lenvatinib, an oral multikinase inhibitor, showed noninferiority in terms of OS compared with sorafenib (median OS duration was 13.6 months for lenvatinib versus 12.3 months for sorafenib) [Kudo, M., et al 2018].

Emerging data of successful immune activation show promising results in various malignancies and provide the opportunity to explore immunotherapy in HCC as a therapeutic approach. Immunotherapy has been shown to produce antitumor effects in HCC, a tumor that has shown resistance to traditional forms of chemotherapy.

Recently, Phase 2 data from treatment with the PD-1 inhibitor, pembrolizumab, in 2L HCC (KEYNOTE-224) were published [Zhu, A. X., et al 2018]. These results included an ORR of 17%, with responses seen in different viral hepatitis subtypes, and several participants with prolonged durations of response. Toxicity was comparable to that seen in participants treated with pembrolizumab in other indications. The Phase 3 2L advanced HCC study comparing pembrolizumab versus placebo (KEYNOTE-240) confirmed these findings, with an ORR of 18%, PFS HR 0.718 (95% CI: 0.570-0.904), and OS HR 0.781 (95% CI: 0.611-0.998) at final analysis [CSR P240V01MK3475 2021]. Although OS and PFS did not meet their statistical endpoints, the data showed a favorable risk benefit profile, and no additional toxicity signals were seen in KEYNOTE-240.

Early data for the combination of lenvatinib and pembrolizumab in advanced HCC are encouraging with respect to both safety and efficacy [Ikeda, M., et al 2018] [Ikeda, M., et al 2019], and a 1L Phase 3 trial LEAP-002 evaluating lenvatinib plus pembrolizumab vs lenvatinib plus placebo in this patient population is ongoing. The current study will evaluate TACE in combination with lenvatinib and pembrolizumab versus TACE plus oral and IV placebos in patients with incurable, nonmetastatic HCC. The showed clinical efficacy and acceptable safety profile of pembrolizumab in HCC, together with single agent activity and safety of lenvatinib in 1L HCC and preliminary safety and efficacy data with the combination, strongly support further development of pembrolizumab and lenvatinib in an earlier treatment setting in combination with TACE.

2.2 Background

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

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.

Refer to the respective IBs for detailed background information on pembrolizumab and lenvatinib.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Lenvatinib

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGRs 1 through 3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. and Hicklin, D. J. 2008] [Tammela, T. and Alitalo, K. 2010]. Accumulated evidence suggests that FGF and its RTK, FGFR, also play important roles in tumor angiogenesis [Cross, M. J. and Claesson-Welsh L. 2001] [Lieu, C., et al 2011] [Limaverde-Sousa, G., et al 2014]. 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 of FGFRs, both of which are currently believed to be very important for tumor angiogenesis. Lenvatinib inhibited VEGF- and FGF-driven proliferation and tube formation of human umbilical vein endothelial cell in vitro. In vivo angiogenesis induced by overexpressed VEGF (KP-1/VEGF transfectants) or FGF (KP-1/FGF transfectants) was significantly suppressed with oral treatments of lenvatinib. Lenvatinib also showed significant antitumor activity in

KP-1/VEGF and in 5 of 7 different types of human tumor xenograft models at between 1 to 100 mg/kg [Yamamoto, Y., et al 2014].

In vitro proliferation assay of 9 human HCC cell lines showed that lenvatinib selectively inhibited proliferation of FGF signal-activated HCC cells, including FGF19-expressing Hep3B2.1-7. Lenvatinib suppressed phosphorylation of FRS2, a substrate of FGFR1–4, in these cells in a concentration-dependent manner. Lenvatinib inhibited in vivo tumor growth in Hep3B2.1-7 and SNU-398 xenografts and decreased phosphorylation of FRS2 and Erk1/2 within the tumor tissue. Lenvatinib also exerted antitumor activity and potently reduced tumor microvessel density in the PLC/PRF/5 xenograft model and 2 HCC patient-derived xenograft models. These results suggest that lenvatinib has antitumor activity across diverse HCC models, and that targeting of tumor FGF signaling pathways and antiangiogenic activity underlies its antitumor activity against HCC tumors [Matsuki, M., et al 2018].

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

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

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

[Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in HCC.

2.2.1.3 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 European Union 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]. The array of disorders associated with metabolic syndrome (eg, obesity, type II diabetes, NAFLD, and nonalcoholic steatohepatitis) are also linked to an increased risk of HCC [Welzel, T. M., et al 2013]. The prevalence of NAFLD in the US ranges from 5.4% to 24% and is the most common reason for abnormal liver function in the US [Abd El-Kader, S. M. 2015]. Surveillance, Epidemiology, and End Results Program data from 2000 to 2011 showed metabolic disorders to be the etiology with the highest population-attributable risk (32%) for the development of HCC in the US [Makarova-Rusher, O. V., et al 2016].

Surgical resection, transplantation, and ablation are potentially curative treatment options for patients with early stage disease; however, about 70% of patients present with 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]. With improved treatment options for HCV, HCC rates are forecast to stabilize in the US over time. However, because a high percentage of HCC in the US is attributed to metabolic disorders, which continue to increase, the overall HCC incidence rates will likely not decrease soon [Petrick, J. L., et al 2016].

TACE has been the mainstay of treating unresectable/unablatable HCC confined to the liver for over 30 years [Guan, Y. S., et al 2012]. It has a dual mechanism of action: delivering chemotherapy directly to the tumor site, and embolizing the arterial blood flow to the tumors,

which supplies most of the HCC nutrients, resulting in tumor necrosis. Currently, 2 main TACE subtypes exist. cTACE uses an embolizing agent, such as lipiodol, in a slurry with a single chemotherapeutic agent. DEB-TACE uses microbeads dipped in chemotherapy, most frequently doxorubicin and epirubicin, to both embolize the tumor vasculature and deliver the chemotherapy to the tumor site. There is no clear clinical advantage of using DEB-TACE over cTACE [Golfieri, R., et al 2014].

Lenvatinib was approved in Japan, US, EU, and China for first-line treatment of unresectable HCC (see Section 2.2.1.5 for additional information). In addition, multiple other new agents have recently been approved for 2L therapy of HCC, including pembrolizumab and nivolumab. Regorafenib and cabozantinib are the only globally approved 2L therapies following 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 recently reported a positive trial 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 showed improved survival, the benefits remain modest, with associated side effects, and they have not shown efficacy in combination with TACE.

2.2.1.4 Immunotherapy Interventions in HCC

As described above, HCC often develops in the setting of various types of liver inflammation. In a gene-expression profiling study, nontumoral tissue from patients with HCC with an inflammatory signature predicted worsened OS [Hoshida, Y., et al 2008]. HCC patients with higher tumor expression of PD-L1 have a significantly poorer prognosis than patients with lower expression [Gao, Q., et al 2009]. In addition, high expression levels of PD-1 on T-cells (both tumor-infiltrating lymphocytes and peripheral blood mononuclear cells) also correlate with higher recurrence rates in HCC patients after surgical resection [Shi, F., et al 2011].

Recently, as described above, immunotherapy has been shown to produce antitumor effects in HCC, a tumor which has shown resistance to traditional forms of chemotherapy. CTLA-4 inhibition with tremelimumab was evaluated in a small study of HCV-associated HCC patients [Sangro, B., et al 2013]. Seventeen patients were evaluable for response, and 3 PRs were seen, lasting for 3.6, 9.2, and 15.8 months. SD was the best response seen in 59%, and of these, 45% were stable for over 6 months. Toxicity was manageable, despite early elevations in transaminases.

A Phase 1/2 study of the anti-PD-1 antibody, nivolumab, in participants with advanced HCC showed an ORR by BICR in the dose-expansion cohort of 19%, and an estimated survival rate in evaluable patients of 83% at 6 months and 74% at 9 months with several durable responses [El-Khoueiry, A. B., et al 2017]. Responses were seen both in viral-mediated HCC and those without an underlying viral etiology. Responses were also seen in those with tumors positive or negative for PD-L1 tumor staining by immunohistochemistry. Results also showed the safety profile of nivolumab in HCC to be generally consistent with that previously reported in other tumor types, and no MTD has been identified [El-Khoueiry, A. B., et al 2017]. As discussed above, early data suggest comparable results with pembrolizumab in advanced HCC.

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

HCC stimulates the development of arterial vessels in the process of progression, and it also expresses high levels of VEGF [Yamaguchi, R., et al 1998] [Poon, R. T. P., et al 2004]. An angiogenesis inhibitor, therefore, which selectively inhibits VEGF receptors, could selectively treat HCC with less effect on background hepatic disease. While lenvatinib is expected to induce tumor necrosis and suppression of progression by inhibiting angiogenesis and blocking blood flow in HCC with high expression of VEGF, an additional incremental benefit (compared with conventional anticancer agents) is that lenvatinib may have the potential for lower levels of toxicity in patients with HCC who have chronic hepatic disease. Because it selectively affects blood vessels, lenvatinib may also be less likely to induce resistance after long-term treatment since endothelial cells are unlikely to become resistant. Lenvatinib has a different TKI profile than sorafenib, inhibiting FGFR pathways in addition to VEGFR pathways, which may contribute to additional antitumor activity in patients with HCC.

Lenvatinib is currently being evaluated in several clinical trials, including patients with HCC, renal cell carcinoma, NSCLC, endometrial cancer, glioma, melanoma, and ovarian cancer (see lenvatinib IB [Kudo, M., et al 2018]). Lenvatinib was approved by Japan (on 23-MAR-2018), FDA (on 15-AUG-2018), the European Commission (on 20-AUG-2018), and China (04-SEP-2018) for first-line treatment of unresectable HCC based on results from the open-label Phase 3 clinical trial E7080-G000-304 (REFLECT) study [Kudo, M., et al 2018]. In data published from the REFLECT study, 954 patients 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 versus 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 (24.1% versus 9.2%), PFS (7.4 months versus 3.7 months), and median TTP (8.9 months versus 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 erythrodysaesthesia (128 [27%] versus 249 [52%]), but an increased frequency of hypertension (201 [42%]) versus 144 [30%]) [Kudo, M., et al 2018].

Recently, Phase 2 data from treatment of 104 participants with pembrolizumab in 2L HCC (KEYNOTE-224) were published [Zhu, A. X., et al 2018]. These results included an ORR of 17%, with responses seen in different viral subtypes, and several participants with prolonged durations of response. The best overall responses were 1 CR (1%), 17 PRs (16%), 46 SD (44%), 34 PD (33%), and 6 (6%) participants who did not have a postbaseline assessment on the cutoff date and were considered not to be assessable. 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.

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 on the basis of 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 clear 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=0.0022) at final analysis, with median PFS of 3.0 months in the pembrolizumab arm versus 2.8 months in the placebo arm. ORR was consistent with KEYNOTE-224 at 18.3% in the pembrolizumab arm versus 4.4% in the placebo 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 AST increased (13.3% vs. 7.5%), blood bilirubin increased (7.5% vs. 5.2%), ascites (7.2% vs. 6.0%), ALT increased (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%) participant treated with placebo, the most common of which were hypothyroidism, hyperthyroidism, pneumonitis, and colitis.

cTACE has been performed since the 1970s as the main modality of therapy for incurable, nonmetastatic HCC. A recent systematic review of literature (n=10,108) showed a median OS of 19.4 months [Lencioni, R., et al 2016]. The most recent Phase 3 TACE trial of orantinib plus TACE versus TACE (ORIENTAL) showed a median OS of 32.3 months on the placebo arm [Kudo, M., et al 2018]. PFS in TACE trials is somewhat variable, but in a large Phase 3 trial of sorafenib plus TACE versus TACE (TACE-2), the median PFS for TACE was 7.8 months [Meyer, T., et al 2017].

cTACE utilizes an embolizing agent, usually lipiodol, in combination with a chemotherapy agent, most frequently doxorubicin. Introduced in the 2000s, DEB-TACE uses drug-eluting microbeads, most frequently in the 100-300 µm range mixed with doxorubicin. Repeated studies have found no differences in efficacy between DEB-TACE and cTACE, though there may be some minor safety advantages to the former [Melchiorre, F., et al 2018] [Golfieri, R., et al 2014]. There is no consensus among interventional radiologists or hepatologists today regarding these 2 modalities. There is general consensus that cTACE should be performed with only one chemotherapy agent. Trials using multichemotherapy cocktail TACE did not show any improvement in efficacy with increased toxicity [Sahara, S., et al 2012] [Gomes, A. S., et al 2017].

2.2.1.6 Scientific Rationale for the Combination of Lenvatinib, Pembrolizumab, and TACE

In preclinical models, lenvatinib decreased the tumor-associated macrophage population, which is known as an immune regulator in the tumor microenvironment. By decreasing tumor-associated macrophages, expression levels of cytokines and immune-regulating receptors were changed to increase immune activation [Kimura, T., et al 2018]. The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/PD-L1 signal inhibitors. The effect of combining lenvatinib with anti-PD-1/PD-L1 mAbs has been investigated in the CT26 colorectal cancer syngeneic model (anti-PD-L1 mAb) as well as the LL/2 lung cancer syngeneic model (anti-PD-1 mAb). Combination treatment with lenvatinib and either an anti-PD-1 or anti-PD-L1 mAb showed significant and superior antitumor effects compared with either compound alone in these 2 syngeneic models [Kato, Y., et al 2015].

Antitumor activity of combination treatment of lenvatinib with anti-PD-1 mAb was also examined in H22 murine HCC cell syngeneic model. The result showed that combination treatment with lenvatinib and anti-PD-1 mAb was more effective than single agent treatment in this model [Kato, Y., et al 2016].

Based on these results, an open-label, Phase 1b/2 study (Study E7080-A001-116) and a Phase 3 study (LEAP-002) to assess the safety and preliminary antitumor activity of the combination of lenvatinib plus pembrolizumab in participants with unresectable HCC is currently ongoing.

The primary mechanism of action of TACE is embolization of the vasculature that feeds HCC tumors, thereby resulting in tumor necrosis. Lenvatinib is an anti-angiogenic drug which should combine to prevent neovascularization of HCC tumors that have received TACE, further magnifying the TACE effect. The resulting necrosis should attract macrophages and other antigen presenting immune cells, potentially further stimulating the immune system disinhibited by the anti-PD-1 effect of pembrolizumab.

2.2.1.7 Clinical Data on Lenvatinib in Combination With Pembrolizumab for Treatment of Solid Tumors and HCC

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Data presented at the European Society of Medical Oncology in 2019 of 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 encouraging initial data [Llovet, J. M., et al 2019]. 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, 30-JUN-2019, 104 patients were enrolled (Part 1, n=6; Part 2, n=61). There was a manageable safety profile for the combination and notable antitumor activity. The ORR, excluding unconfirmed responses, for the first 67 patients was 46.3% by mRECIST and 32.8% by RECIST 1.1 as assessed by BICR. See Section 4.3 – Justification for Dose for additional information.

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

Refer to the respective IBs for preclinical and clinical study data for pembrolizumab 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 2.2.1.2, both lenvatinib, pembrolizumab (alone and in combination) and TACE, have shown promising efficacy in participants with HCC, and preliminary safety data of the combination of lenvatinib and pembrolizumab suggest toxicity is manageable. Given the limited treatment options for patients with incurable, nonmetastatic HCC, there is an unmet medical need for novel therapies in this setting. Inhibiting angiogenesis in combination with TACE and the addition of PD-1 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 checkpoint 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 IBs and ICF documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, throughout this protocol, the term RECIST 1.1 refers to an adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Additionally, new intrahepatic lesions must meet LI-RADS 5 criteria (Appendix 13) to be considered unequivocal as per RECIST 1.1. Refer to Section 4.2.2.1 for further details.

In 1L therapy of participants with incurable/nonmetastatic HCC:

Objectives	Endpoints
Primary	
• Objective: To compare pembrolizumab plus lenvatinib in combination with transarterial chemoembolization (TACE) vs. placebo plus TACE with regard to progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) assessed by blinded, independent central review (BICR) • Hypothesis (H1): Pembrolizumab plus lenvatinib in combination with TACE is superior to placebo plus TACE with respect to PFS per RECIST 1.1 assessed by BICR	• PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
• Objective: To compare pembrolizumab plus lenvatinib in combination with TACE vs. placebo plus TACE with regard to overall survival (OS) • Hypothesis (H2): Pembrolizumab plus lenvatinib in combination with TACE is superior to placebo plus TACE with respect to OS	• OS: the time from randomization to death due to any cause

Objectives	Endpoints
Secondary	
• Objective: To evaluate pembrolizumab plus lenvatinib in combination with TACE vs. placebo plus TACE with regard to PFS, objective response rate (ORR), disease control rate (DCR), duration of response (DOR) and time to progression (TTP) per modified RECIST (mRECIST) assessed by BICR	• PFS • OR: complete response (CR) or partial response (PR) • Disease control (DC): a best overall response of CR, PR, or stable disease (SD) • DOR: the time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first • TTP: the time from randomization to the first documented disease progression
• Objective: To evaluate the safety and tolerability of pembrolizumab plus lenvatinib in combination with TACE versus placebo plus TACE	• Adverse Events (AEs), serious adverse events (SAEs), and hepatic AEs • Study intervention discontinuations due to AEs
• Objective: To evaluate pembrolizumab plus lenvatinib in combination with TACE versus placebo plus TACE with regard to efficacy outcomes per RECIST 1.1 assessed by BICR	• OR, DC, DOR, and TTP
Tertiary/Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	
• Objective: To evaluate pembrolizumab plus lenvatinib in combination with TACE versus placebo plus TACE with regard to score change from baseline of health-related quality of life (HRQoL) and to evaluate time to deterioration (TTD) using the European Organisation for Research and Treatment of Cancer Quality of Lift Questionnaire – Core v 3.0 (EORTC QLQ-C30) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Hepatocellular Carcinoma Module (EORTC QLQ-HCC18).	• Global scores of the EORTC QLQ-C30 and EORTC QLQ-HCC18. • TTD: the time to first onset of a 10 point or more decrease from baseline. TTD evaluated for EORTC QLQ-C30 and EORTC QLQ-HCC18 global health status/QoL. Details will be provided in a supplemental statistical analysis plan (sSAP).
• Objective: To characterize pembrolizumab plus lenvatinib in combination with TACE versus placebo plus TACE with regard to health utilities using EuroQol-5-Dimension, 5-Level Questionnaire (EQ-5D-5L).	• EQ-5D-5L health utility score

The study will be deemed positive if either OS or PFS null hypotheses are rejected.

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, randomized, active-controlled, parallel-group, double-blind study of lenvatinib plus pembrolizumab in combination with TACE versus oral placebo plus IV placebo in combination with TACE in 1L intervention in participants with incurable/nonmetastatic hepatocellular carcinoma. Approximately 450 participants will be randomized in a 1:1 ratio to the following 2 treatment groups:

- Arm A: Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally QD plus pembrolizumab 400 mg IV Q6W plus TACE

- Arm B: Oral placebo QD plus IV placebo (normal saline) Q6W plus TACE.

Lenvatinib dosing is based on actual body weight at screening. Pembrolizumab/placebo will be administered Q6W for up to 2 years. Each cycle is Q3W from Cycle 1 through Cycle 4 and Q6W thereafter (ie, Cycle 5 and beyond, or from Cycle 4 if pembrolizumab/placebo is administered C4D1 due to treatment delay). Participants who require more frequent medical assessments may be scheduled for Q3W visits at the discretion of the investigator. Lenvatinib/oral placebo will be administered until PD or unacceptable toxicity. TACE will CCI [redacted]
This protocol does not allow participants to cross over to the other arm if they experience progression.

The primary objectives of this study are to compare the PFS and OS of lenvatinib plus pembrolizumab plus TACE versus placebo (IV and oral) plus TACE per RECIST 1.1 assessed by BICR. On study imaging assessments will be performed Q9W calculated from the date of randomization and independent of treatment delays. RECIST 1.1 will be used by the site for treatment decisions until the first radiologic evidence of PD. PD will also be confirmed by the BICR vendor. Participants who experience confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted approximately every 12 weeks or more frequently to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Following the last inferential analysis for the study, participants who discontinued study treatment or are receiving placebo will be discontinued from the study. Participants who are on lenvatinib therapy may be enrolled in an extension study.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3 (Table 1). Details of each procedure are provided in Section 8.

The risks of solid organ transplant following treatment with PD-1 inhibitor therapy have not been extensively studied. The timeframe for safe or appropriate liver transplantation after the last dose of pembrolizumab is unknown. Therefore, it is recommended not to perform liver transplantation within at least 120 days (5 half-lives) of stopping pembrolizumab. The risks and benefits of transplant should be discussed with the participant by the treating investigator.

This study will use a group sequential design, using an independent eDMC to monitor safety and efficacy. CCI [redacted]

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Results of IA will be reviewed by the eDMC, who will make recommendations to the Sponsor to continue, modify, or end the study according to the plan described briefly in Section 10.1.4.3 and in detail in Section 9 – Statistical Analysis Plan.

4.2 Scientific Rationale for Study Design

The LEAP-012 trial is designed for the unresectable/incurable HCC patient population, for whom TACE is the standard of care. Participants are randomized 1:1 between TACE and pembrolizumab plus lenvatinib in combination with TACE to determine the OS and PFS advantage of adding this study intervention combination to the current standard of care. Based on preliminary Study E7080-J081-116 (MK-3475-524) data [Llovet, J. M., et al 2019], it is anticipated that pembrolizumab plus lenvatinib will become a new standard for systemic treatment of HCC. Pembrolizumab and lenvatinib may potentiate therapeutic efficacy of TACE, and the trial design aims to take advantage of this by administering the study drugs 2 to 4 weeks prior to the first TACE procedure.

4.2.1 Rationale for Stratification Factors

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4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

The study includes primary efficacy endpoints: OS and PFS per RECIST 1.1 as assessed by BICR.

PFS is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression as determined by central review will be communicated to the site.

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. PFS is being included as a primary endpoint because efficacy in PFS may be able to be established earlier than efficacy in OS, and given better efficacy seen in newer HCC therapies it may be a useful surrogate for OS.

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

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4.2.2.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility Section 8.2.1. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

Additionally, new intrahepatic lesions must meet LI-RADS 5 criteria (Appendix 13) to be considered unequivocal as per RECIST 1.1. Patients with HCC, particularly those with underlying cirrhosis, have long been known to develop benign hepatic findings, such as dysplastic and regenerative nodules, that may radiographically resemble HCC. Distinguishing benign findings from HCC is particularly important in intermediate stage disease, where a relatively long PFS increases the likelihood that new benign findings will appear during the course of the clinical trial. The proposed use of LI-RADS 5 to define new lesions is intended to mitigate the risk of mis-categorizing benign findings as new HCC lesions.

4.2.2.1.2 mRECIST

mRECIST 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 8.2.1.5.

4.2.2.2 Safety Endpoints

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

4.2.2.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities. As part of the analyses for this study, participants will provide information regarding their HRQoL via the following assessment tools: EORTC QLQ-C30, EORTC QLQ-HCC18, and/or EQ-5D-5L questionnaires. The EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D-5L PROs are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.2.3.1 EORTC QLQ-C30

EORTC QLQ-C30 is the most widely used cancer-specific, health-related, QoL 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. The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies [Aaronson, N. K., et al 1993].

4.2.2.3.2 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 (Quality of Life Group) designed for use in clinical trials, 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.

4.2.2.3.3 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].

4.2.2.4 Pharmacokinetic Endpoints

Based on PK data obtained in this study and from other studies, a population PK analysis will be performed to characterize PK parameters of pembrolizumab when co-administered with lenvatinib and TACE to support the proposed dosing regimen.

4.2.2.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.2.6 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies, including novel combination with antiangiogenesis therapy, is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. CCI

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Other blood-derived biomarkers

CCI [redacted]

Assays such as enzyme-linked immunosorbent assay (ELISA) measure such proteins in serum. CCI [redacted]

CCI [redacted]

4.2.3 Rationale for the Use of Comparator/Placebo

Participants will be randomized to receive pembrolizumab plus lenvatinib (Arm A) or IV placebo plus oral placebo (Arm B). Both treatment arms will receive TACE. Cross over will not be allowed at any time.

TACE is the current standard of care for unresectable, nonmetastatic HCC without portal vein thrombosis, as per AASLD and ESMO guidelines [Marrero, J. A., et al 2018] [Vogel, A., et al 2018]. Previous Phase 3 trials combining TKIs with TACE, including sorafenib in TACE-2 and SPACE trials [Meyer, T., et al 2017] [Lencioni, R., et al 2016], brivanib [Kudo, M., et al 2014], and orantinib [Kudo, M., et al 2018] have all failed to show improvement in OS. Since cTACE and DEB-TACE have been proven equally efficacious in previous trials [Golfieri, R., et al 2014] [Song, J. E. 2017], both will be permitted on this protocol. To remove potential intrasite bias, each site will be required to select the method of TACE (cTACE versus DEB-TACE) and chemotherapy agent (Section 8.1.8.1.1) that will be used for all participants at that site prior to initiating the study.

To maintain study blinding, both oral and IV placebos will be used, for lenvatinib and pembrolizumab, respectively.

4.3 Justification for Dose

4.3.1 Pembrolizumab

Participants may receive pembrolizumab 400 mg or IV placebo Q6W for up to 2 years (approximately 17 doses).

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 appropriate [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:
    - C_{avg} over the dosing interval or AUC at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
    - C_{min} at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of participants.

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

4.3.2 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 body weight. The decrease in CL/F in participants with low body weight 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 treatment-emergent AEs (TEAEs) was similar for participants treated with either starting dose [Kudo, M., et al 2018]. These findings support the appropriateness of the lower starting dose of 8 mg for participants with BW <60 kg. Lenvatinib has subsequently received approval in most major world markets for this dosing as 1L therapy for advanced HCC.

Study E7080-J081-116 (MK-3475-524) is a Phase 1b study to evaluate the tolerability and safety of lenvatinib (8 mg for participants <60 kg BW and 12 mg for participants ≥60 kg BW, orally) in combination with pembrolizumab (200 mg IV) in patients with unresectable HCC [Ikeda, M., et al 2018]. Tolerability was evaluated by assessing DLTs during the first cycle in participants who were ineligible for other therapies (3+3 design; Part 1). Once tolerability of lenvatinib plus pembrolizumab was confirmed, additional participants with no prior systemic therapy for unresectable HCC were enrolled (Part 2). As of 22-MAR-2018, 30 participants were enrolled in the study (Part 1, n=6; Part 2, n=24) [Ikeda, M., et al 2018]. Participants had BCLC Stage B (n=9) or Stage C (n=21), CP scores of 5 (n=26) or 6 (n=4), and 4 participants (13.3%) had received prior sorafenib. No DLTs were reported in Part 1, and the MTD was determined as lenvatinib 12 mg (≥60 kg BW) or 8 mg (<60 kg BW) orally QD in combination with pembrolizumab 200 mg IV Q3W. The toxicity profile for the combination was manageable. The most common TEAEs were decreased appetite (53.3%), hypertension (53.3%), diarrhea (43.3%), and fatigue (40.0%). The best overall response per investigator assessment by mRECIST was Part 1, PR (n=4, 66.7%) and SD (n=2, 33.3%) and Part 2, CR

(n=1, 5.0%), PR (n=6, 30.0%), and SD (n= 13, 65.0%). The ORR (excluding unconfirmed responses) for Part 1 was (n=3, 50.0%) and (n=4, 20.0%) for Part 2. This study was expanded to a Phase 2 and has completed accrual of 104 participants on 11-APR-2019. No additional toxicities have been noted, and a Phase 3 study evaluating lenvatinib vs lenvatinib plus pembrolizumab in advanced HCC is currently ongoing using this dosing of lenvatinib (LEAP-002).

4.3.3 Maximum Dose/Exposure for This Study

The maximum dose for lenvatinib or oral placebo is 12 mg/day. Lenvatinib or oral placebo will be continued until discontinuation by the investigator, disease progression, or unacceptable toxicity. The maximum dose/exposure of pembrolizumab or IV placebo allowed in this study is 400 mg Q6W up to 2 years (approximately 17 doses).

TACE may be performed up to 2 times per lesion. All HCC tumors must be amenable to TACE within 2 sessions. Therefore, the maximum number of TACE procedures is 2 for participants whose lesions may all be treated with 1 procedure, and 4 for participants who require split-TACE.

4.4 Beginning and End of Study Definition

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

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

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

Following the last inferential analysis for the study, participants who discontinued study treatment or are receiving placebo will be discontinued from the study. Participants who are on lenvatinib therapy may be enrolled in an extension study.

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

Male/female participants with incurable/nonmetastatic HCC will be enrolled in this study.

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

Refer to Appendix 7 for country-specific criteria.

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

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

- Has a radiologic diagnosis of HCC as per the AASLD guidelines (Appendix 13), which requires:
  - liver cirrhosis AND
    - a liver mass confirmed by BICR 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

  Note: If the BICR is unable to confirm HCC diagnosis by AASLD guidelines (Appendix 13), but finds the participant eligible on other parameters, the BICR will notify the site of the need for diagnosis by pathology. These participants will require a histologic or cytologic diagnosis of HCC prior to randomization.

2. Has HCC localized to the liver without portal vein thrombosis, and not amenable to curative treatment such as resection, ablation, or liver transplant. No extrahepatic HCC is permitted, confirmed by BICR.

3. Has at least one measurable HCC lesion based on RECIST 1.1, confirmed by BICR.

4. Has all lesions treatable with TACE in 1 or 2 (split-TACE) sessions.

5. Is amenable, without any contraindications, to the TACE procedure and chemotherapy agent prespecified at the study site.

6. Has a CP class A liver score within 7 days prior to first dose of study intervention (see Appendix 10).

7. Has a predicted life expectancy of >3 months.

Demographics

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

9. Is male or female ≥18 years of age at the time of signing the informed consent.

Male Participants

10. Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

    - Lenvatinib 7 days

    - TACE 95 days

      Note: Refer to Appendix 7 for country-specific criteria.

- Refrain from donating sperm

  PLUS either:

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

  OR

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

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

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

Female Participants

11. 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 the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:

  - Pembrolizumab 120 days
  - Lenvatinib 30 days
  - TACE 180 days

  The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or 72 hours for serum before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
  - Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.2.
  - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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

Informed Consent

12. The participant (or legally acceptable representative if applicable) has provided documented informed consent/assent for the study. Note: Refer to Appendix 7 for German-specific criteria.

Additional Categories

13. Participants with past or ongoing HCV infection will be eligible for the study. Treated participants must have completed their treatment at least 1 month prior to starting study intervention.

14. Participants with HBV will be eligible as long as they meet the following criteria:

    - Participants on active HBV therapy should stay on the same therapy throughout study intervention.
    - Participants who are CCI [redacted]
    - Participants CCI [redacted]

    Note: Refer to Appendix 7 for country-specific criteria.

15. 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.

16. Has adequate organ function as defined in the following table (Table 2). Specimens must be collected within 7 days prior to the start of study intervention.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥75,000/µL
Hemoglobin	≥8.0 g/dL without transfusion or EPO dependency[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥40 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤2 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >2 × ULN
AST (SGOT) and ALT (SGPT)	≤5 × ULN
Amylase and lipase	≤1.5 × ULN
Albumin[3]	>3.0 g/dL
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT)	≤2 OR ≤1.5 × ULN

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

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

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

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

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has HCC lesion(s) measuring ≥10 cm in any dimension, has more than 10 lesions on radiographic evaluation or has HCC lesions occupying ≥50% of the liver volume, confirmed by BICR.

2. Is currently a candidate for liver transplantation.

3. 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 the first dose of study intervention. 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 prior to first dose of study intervention are excluded.

4. Has bleeding or thrombotic disorders or is using anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with antiplatelet agents and low molecular weight heparin is permitted.

5. Has clinically apparent ascites on physical examination that is not controlled with medication.

   Note: Ascites detectable on imaging studies only are allowed.

6. Has any macrovascular tumor thrombosis in the portal veins, confirmed by BICR.

   Note: microvascular tumor thrombosis detected on biopsy, but not radiographic scan, is permitted.

7. 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 excluded.

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

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

10. Has a pre-existing Grade ≥3 gastrointestinal or nongastrointestinal fistula.

11. Has clinically significant hemoptysis from any source or tumor bleeding within 2 weeks prior to the first dose of study intervention.

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

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

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

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

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

16. Has HAP score D (see Appendix 14).

Prior/Concomitant Therapy

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

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

19. Has received locoregional therapy to existing liver lesions (such as TACE, transarterial embolization, TARE, hepatic arterial infusion, or radiation,) for treatment of HCC. Previous use of ablation and resection are permitted if >4 weeks prior to first dose of study intervention. Previous use of other locoregional therapy to lesions that have resolved is permitted if >6 months prior to first dose of study intervention.

20. Has received a live vaccine within 30 days prior to the first dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are permitted; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not permitted. Refer to Section 6.5.2 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

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

23. Has a 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.

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

25. 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 [eg, ≤10 mg prednisone] for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted.

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

27. Has an active infection (including tuberculosis) requiring systemic therapy, with the exception of HCV or HBV.

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

29. Participants with proteinuria >1+ on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24 hours will be ineligible.

30. Has prolongation of QTc interval to >480 ms (corrected by Fridericia Formula).

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

32. Has dual active HBV infection CCI [redacted] and HCV infection CCI [redacted]

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

34. 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

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Contraception

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies of pembrolizumab and lenvatinib will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 3.

Country-specific differences are noted in Appendix 7.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Form-ulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
Arm A	Experimental	Lenvatinib	Drug	Capsule	4 mg	12 mg (BW ≥60 kg) or 8 mg (BW <60 kg)	Oral	Once daily, up to 2 years	Test Product	IMP	Centrally by Sponsor
Arm A	Experimental	Pembrolizumab	Drug	Vial	25 mg/mL	400 mg	IV Infusion	Q6W; up to 2 years	Test Product	IMP	Centrally by Sponsor
Arm A	Experimental	TACE	Procedure/Surgery	N/A	Variable	Variable	Intra-arterial	≥1 month between TACE, max 4 TACE	Background Treatment	NIMP/AxMP	Sourced by Site
Arm B	Active Comparator	Oral Placebo	Drug	Capsule	N/A	N/A	Oral	Once daily, up to 2 years	Placebo	IMP	Centrally by Sponsor
Arm B	Active Comparator	IV Placebo	Drug	Vial	Normal Saline, 0.9% w/v	0 mg	IV Infusion	Q6W; up to 2 years	Placebo	IMP	Locally by Study Site, subsidiary, or designee
Arm B	Active Comparator	TACE	Procedure/Surgery	N/A	Variable	Variable	Intra-arterial	≥1 month between TACE, max 4 TACE	Background Treatment	NIMP/AxMP	Sourced by Site

BW = body weight; IMP = investigational medicinal product; IV = intravenous; max = maximum; N/A = not applicable; NIMP/AxMP = noninvestigational/auxiliary medicinal product; Q6W = every 6 weeks; TACE = transarterial embolization.

a Lenvatinib dosing is based on actual body weight at screening and will be fixed for the duration of the study.

b Hold lenvatinib/oral placebo 2 days pre- and at least 7 days post-TACE.

c Participants who complete 2 years of treatment may continue to receive lenvatinib/placebo alone until progression or intolerable toxicity.

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 European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis unless hospitalization is required for TACE.

All products indicated in Table 3 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements with the exception of IV placebo (normal saline), which will be provided locally.

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.

The oral placebo was created by the Sponsor and Eisai to match the active product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab or IV placebo will be provided separately. Lenvatinib and oral placebo are both capsules for oral administration and do not require preparation.

If a dose of lenvatinib/oral placebo 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.

TACE components to be stored and the procedure to be administered are per site SOPs.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to TACE + lenvatinib + pembrolizumab study intervention or TACE + oral placebo + IV placebo.

6.3.2 Stratification

CCI



CCI

[redacted]

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. Pembrolizumab and placebo (normal saline) will be packaged identically by site pharmacy so that the blind is maintained. Lenvatinib will be packaged identically to the matching oral placebo so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Administration of pembrolizumab/IV placebo will be witnessed by the investigator and/or study staff, and/or qualified designee per institutional guidelines and procedures. Interruptions from the protocol-specified treatment plan for >28 days for lenvatinib or oral placebo or >12 weeks for pembrolizumab or IV placebo require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Lenvatinib/placebo 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.

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.

6.5.1 Allowed Concomitant Medications

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control or symptom management is not permitted during the study.

6.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during Screening and the Study Intervention 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 pembrolizumab or lenvatinib

- Locoregional therapy (other than TACE as specified in the protocol)

- Radiation therapy

- Live vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Refer to Appendix 7 for country-specific requirements.

  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 (eg, ≤10 mg prednisone) may be approved after consultation with the Sponsor. Exception: steroids may be used for premedication prior to imaging.

- Anticoagulants that require INR monitoring, such as warfarin. Treatments that do not require INR monitoring, such as low molecular weight heparin and antiplatelet agents, are permitted.

Participants who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study intervention.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, OTC products, herbal supplements, and IV medications and fluids. If changes

occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.7.

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 truly 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.

Listed below are specific restrictions for concomitant therapy during the course of the study.

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

Herbal Supplements/Alternative Medicines

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

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

There are no prohibited therapies during the Poststudy Intervention Follow-up Phase.

6.5.3 Drug-Drug Interaction

There are no DDI-related concomitant medication prohibitions or restrictions

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

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

No drug interaction is expected between pembrolizumab and lenvatinib because of their divergent metabolic pathways. Pembrolizumab is a monoclonal antibody and is primarily

catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and nonenzymatic processes (LENVIMA product information).

6.5.4 Rescue Medications and Supportive Care

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

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 6 in Section 6.6.2 for guidelines regarding dose modification and supportive care for pembrolizumab.

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

6.6 Dose Modification (Escalation/Titration/Other)

AEs will be graded using NCI CTCAE Version 5.0. 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 one drug in the lenvatinib-pembrolizumab combination due to toxicity can continue with the other drug in the combination until criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression).

Refer to Section 6.6.4 for dose modification guidance for overlapping toxicity for the pembrolizumab plus lenvatinib combination.

6.6.1 Lenvatinib Dose Modification

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose-modification guidelines described in Table 4. An interruption of study intervention for more than 28 days will require Sponsor approval before treatment can be resumed.

Additionally, lenvatinib/oral placebo must be held 2 days prior to each TACE procedure and for at least 7 days after the TACE procedure. Lenvatinib/oral placebo may be resumed after resolution of postembolization syndrome, with AEs improved to Grade 1 or baseline. TACE toxicity management will be conducted per local standard of care.

The starting dose of lenvatinib/oral placebo 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 4. Once the dose has been reduced, it cannot be increased at a later date unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Table 4 Dose Modification for Lenvatinib Treatment-Related Toxicity

	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 6.6.1.1), proteinuria (Section 6.6.1.2), diarrhea (Section 6.6.1.3), thromboembolic events (Section 6.6.1.4), PRES/RPLS (Section 6.6.1.5), hypocalcemia (Section 6.6.1.6), hemorrhage (Section 6.6.1.7), and gastrointestinal perforation or fistula (Section 6.6.1.8), as appropriate, before consulting the dose modification table (Table 5).

Table 5 Dose Modification Guidelines for Lenvatinib-related Adverse Events (for the Lenvatinib-Pembrolizumab 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 (same toxicity or new toxicity)[g]	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	

Note: For grading see CTCAE version 5.0. Collect all CTCAE grades of AEs, including decreasing and increasing grades.

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

b Initiate optimal medical management for nausea, vomiting, hypothyroidism, and/or diarrhea prior to 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 reach at least a minimum BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.

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/matching placebo. See Section 6.6.1.4.

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.

6.6.1.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that all participants enrolled 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 Cycle 1 Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 1.3). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the participant's first BP measurement at the current assessment time point is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as one BP assessment. 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. One BP assessment is defined as the mean value of 2 measurements at least 5 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/matching placebo 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 with 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.

A diary will be provided to the participant to capture the BP evaluations between study visits.

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

- Continue study intervention and institute antihypertensive therapy for participants not already receiving this.

- 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.
- If systolic BP is ≥160 mm Hg or diastolic BP is ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
  - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
  - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
  - Additional dose reduction should be discussed with the Sponsor.

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

1. Institute appropriate medical management
2. Discontinue study intervention

6.6.1.2 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, 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 5.

- In the event of nephrotic syndrome, lenvatinib must be discontinued

Detection and Confirmation

1. Perform urine dipstick testing per the SoA (Section 1.3)

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+ proteinuria on urine dipstick while on study drug
   - A subsequent increase in severity of urine dipstick 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+

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 testing for participants with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

6.6.1.3 Management of Diarrhea

An antidiarrheal agent should be recommended to the participant at the start of lenvatinib/oral placebo 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 5 should be followed.

6.6.1.4 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis signs including lower-extremity swelling, and warmth to touch or tenderness. If any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 5

should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, lenvatinib/oral placebo 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/oral placebo discontinuation.

6.6.1.5 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 5 should be followed.

6.6.1.6 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.

6.6.1.7 Management of Hemorrhage

Instructions in Table 5 (Nonhematologic Toxicities) should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib/oral placebo depending on the severity and persistence of hemorrhage.

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

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

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

Dose Modification and Toxicity Management Guidelines for Nonhepatic irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6. Dose modification, diagnosis, and management guidance for hepatic events of clinical interest is provided in Section 6.6.3.

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

General instructions:

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

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

[b] Events that require discontinuation include, but are not limited to encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hour to 50 mL/hour). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 hours (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

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

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 6 weeks (42 days) of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.3 Guidance for Management of Hepatic Events of Clinical Interest

HECIs are described in Section 8.4.7. All of these HECIs will require holding study intervention and notification to the Sponsor within 24 hours. All cases of retreatment after interruption of study intervention for HECI must be reported to the Sponsor and recorded in the database. As per Section 8.4.7, HECIs are not the result of disease progression or TACE complications, 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. For laboratory assessments of HECIs, central laboratory is preferred; local laboratory is acceptable if central 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, ALP, 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, HBeAg, anti-HBc (total and IgM), anti-HBe, 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. Immune-related hepatitis has been observed in approximately 1% of participants who received pembrolizumab. 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 lenvatinib/oral placebo and pembrolizumab/placebo 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 Pembrolizumab/Placebo" below.

6.6.3.1 Management of HECI for Lenvatinib Toxicity:

Lenvatinib/Oral Placebo 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 QOD). 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/oral placebo.	Reduce lenvatinib/oral placebo 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/oral placebo.	Reduce lenvatinib/oral placebo 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/oral placebo.	Reduce lenvatinib/oral placebo 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/oral placebo.	Discontinue lenvatinib/oral placebo.

[a] Not applicable for participants who start at 8 mg QD.

6.6.3.2 Management of HECI for Pembrolizumab/ IV Placebo

	Diagnosis	Management
Hepatitis B consider flare or change in HBV immunologic status	Rapid elevation of ALT to >5×ULN and/or >3× baseline	Interrupt pembrolizumab/ IV placebo intervention for **up to 12** weeks. Start antiviral therapy or check for compliance if HBV is detectable. Measure safety labs for AST, ALT, ALP, T Bili, D Bili, and INR on **weekly** basis. Measure HBsAg and HBV DNA on **weekly** basis (if detected at the time of onset of ECI). Evaluate the following every 2 to 3 weeks: • anti-HBe, HBe antigen, anti-HBs, and HBV DNA levels (if not detected at the onset of ECI) Restart pembrolizumab/ IV placebo intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.
Hepatitis C exacerbation in participants with HCV RNA positive	Rapid elevation of ALT to >5×ULN and/or >3x baseline	Interrupt pembrolizumab/ IV placebo intervention for **up to 12** weeks. Assess use of injection or inhalation drugs. Recheck HCV genotype at the time of relapse of HCV RNA to rule out new infection. Measure safety labs for AST, ALT, ALP, T Bili, D Bili, and INR on **weekly** basis Measure HCV RNA levels **every 2 weeks.** Please discuss risk benefit with Sponsor prior to starting HCV antiviral therapy. Restart pembrolizumab/ IV placebo intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.
Relapse of HCV infection for participants with successfully treated or new HCV infection	If HCV RNA was TND at baseline, and now has confirmed detectable HCV RNA (2 specimens, 1 week apart)	

	Diagnosis	Management
Immune-related Hepatitis	If any of the HECI criteria is met as defined in the protocol Section 8.4.7 Note: Immune-related hepatitis is a diagnosis made after excluding other possible etiologies such as viral flare, biliary or vascular obstruction, infection, medications, and alcohol use; usually immune-related hepatitis response to dechallenge and/or steroids and re-occurs with rechallenge	Interrupt pembrolizumab/ IV placebo study treatment for **up to 12 weeks.** Start IV corticosteroid 60 mg/day of prednisone or equivalent followed by oral corticosteroid. Monitor with biweekly laboratory tests, including AST, ALT, T Bili, D Bili, ALP, and INR. **Restart pembrolizumab/ IV placebo intervention only if:** a) Abnormal laboratory values resolve to Grade ≤1 or baseline (if abnormal at baseline) b) Taper steroid over 28 days c) Steroid treatment is tapered to prednisone ≤10 mg/day or equivalent **Permanently discontinue pembrolizumab/ IV placebo intervention if:** a) Laboratory abnormalities do not resolve within 6 weeks b) Steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks c) Decompensation to CP-C status
Other Causes	Rule out infection with blood, urine, and ascites culture – antibiotics should be started if infection is found If total bilirubin is elevated, imaging should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression by imaging Rule out alcohol use and hepatotoxic drugs including herbal and alternative medications	Restart pembrolizumab/IV placebo only if laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade **within 6 weeks.** If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.

ALP = alkaline phosphatase; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antigen antibody; ALT= alanine aminotransferase; AST = aspartate aminotransferase; CP-C = Child-Pugh Grade C; D Bili = direct bilirubin; DNA = deoxyribonucleic acid; HBeAg = hepatitis B e antigen, HBV = hepatitis B virus; INR = international normalized ratio; IV = intravenous; T Bili = total bilirubin; TND = target not detected .

6.6.4 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as 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 drug most likely related to the AE, or an

alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

Since lenvatinib/oral placebo is dosed daily and continuously due to a relatively short half-life (~ 28 hours), and pembrolizumab is dosed Q6W due to a long half-life (20 days), lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

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

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

Lenvatinib/oral placebo will be held 2 days prior and at least 7 days after each TACE procedure. It may be resumed once postembolization syndrome has resolved, and all AEs associated with TACE have resolved to Grade 0-1 or baseline. TACE toxicity management will be conducted per local standard of care.

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 study drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

6.6.5 Other Allowed Dose Interruptions

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

- For minor procedures: stop lenvatinib/oral placebo 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/oral placebo at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.

6.6.6 Second Course

This study does not have an extension second course.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention
- The participant has a confirmed positive serum pregnancy test
- Radiographic disease progression outlined in Section 8.2.1
- Any progression or recurrence of any 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), unless related to TACE
  - Drug-related total bilirubin >10 x ULN, unless related to TACE
  - CP score of >9 points if not improved to CP score <9 by therapy
  - Hepatic encephalopathy not manageable by therapy
  - Clinical ascites not manageable by therapy

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.

Following the last inferential analysis for the study, all participants on study intervention will be unblinded, and those on placebo will be discontinued from study. Additionally, following the last inferential analysis for the study, all participants who are discontinued from study intervention will be discontinued from study.

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant

repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

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 enrolled in this study will be recorded separately and not listed as a prior medication.

For all participants with a history of HBV or HCV, 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 prior to randomization. Each participant

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Administration of pembrolizumab or IV placebo will be witnessed by the investigator and/or study staff, and/or qualified designee per institutional guidelines and procedures. Lenvatinib or oral placebo may be administered at home except on Day 1 of Cycles 1 and 3. Please refer to Section 8.1.8.1 for further detail.

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

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 TACE

The interventional radiologist(s) or other qualified physician at each site will perform prespecified TACE (DEB-TACE or cTACE) with the prespecified chemotherapy agent only. DEB-TACE may be performed with epirubicin or doxorubicin, with no prespecified bead size or chemotherapy dosage. cTACE may be performed with epirubicin, doxorubicin or cisplatin, utilizing lipiodol, with no prespecified mixing modality or chemotherapy dosage. Additional hemostatic agents may be used if determined necessary by the treatment team.

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8.1.8.1.2 Lenvatinib/Oral Placebo

Lenvatinib/oral placebo are both provided as 4 mg capsules. Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) (Arm A) or oral placebo (Arm B) QD will be taken orally with water (with or without food) at approximately the same time each day in each cycle.

If a lenvatinib or oral placebo 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.

8.1.8.1.3 Pembrolizumab/IV Placebo

Pembrolizumab (Arm A) or IV placebo (Arm B) 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 or IV placebo may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the discontinuation visit (End of Intervention) 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

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study intervention, the reason

thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding that is part of the study design has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

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

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.11 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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. 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. All images of the liver using triphasic CT submitted after screening must include digital subtraction of the precontrast from the arterial phase images to allow differentiation of enhancement from post-TACE artifacts. 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 demonstrates radiologic progression, should also be submitted to the iCRO.

When the investigator identifies radiographic progression per RECIST 1.1, the iCRO will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor via email (see Section 8.2.1.4). Treatment should continue until PD has been verified by BICR (if initial site-assessed PD was not verified by BICR, each subsequent scan must be submitted to iCRO with verification of PD request until PD has been verified by BICR). Once PD is verified centrally, subsequent imaging (if acquired) should not be submitted to the iCRO.

8.2.1.1 Initial Tumor Imaging

The screening images must be submitted to the iCRO for central verification that the eligibility criteria based on Section 5.1 have been met prior to randomization.

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 prior to the date of randomization and can be assessed by the iCRO.

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days]) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (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 is identified by the investigator and verified by the BICR, 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. Note: Response does not typically need to be verified in real time by the BICR.

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

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

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

8.2.1.4 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 for RECIST 1.1, if clinically relevant to enable a broader sampling of tumor burden.

Initial tumor imaging showing site-assessed PD per RECIST 1.1 should be submitted immediately for BICR verification of PD. The site and Sponsor will be notified whether the BICR verifies PD using RECIST 1.1.

New intrahepatic lesions must meet LI-RADS 5 criteria (Appendix 13) to be considered unequivocal as per RECIST 1.1.

8.2.1.5 Modified RECIST Assessment of Disease

mRECIST 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]. mRECIST will be used by BICR as the secondary measure for assessment of 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.

Although mRECIST 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.

8.2.2 Patient-reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D-5L questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: first the EORTC QLQ-C30, then EORTC QLQ-HCC18, and lastly the EQ-5D-5L. See SoA (Section 1.3) for ePRO administration schedule. A visit window of ±7 days will apply to the PRO visit assessments.

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

If at the time of enrollment of a participant, the translated version of the EORTC QLQ-C30, EQ-5D-5L and/or EORTC QLQ-HCC18 questionnaires are not available for that language/country, then the EORTC QLQ-C30, EQ-5D-5L and/or EORTC QLQ-HCC18 will not be required for this participant until the questionnaire(s) become available for that language/country. The other study PRO measures must be completed as scheduled. Additionally, participants who are illiterate are not required to complete study PROs.

NOTE: For some sites, the translated EORTC QLQ-C30, EQ-5D-5L and/or EORTC QLQ-HCC18 might become available after study startup and should be administered to participants when it becomes available; for some sites, the EORTC QLQ-C30, EQ-5D-5L 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) will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard.

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

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination, including oral examination, during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. 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

A directed physical examination, including oral examination, is required prior to the administration of study intervention as outlined in Section 1.3. 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.

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

Under exceptional circumstances, participants will have the option of having BP measured between visits obtained locally by a health care professional. A diary will be provided as a tool to aid the participant in collecting BP evaluations between study visits.

8.3.3 Electrocardiograms

ECGs will be obtained as designated in the SoA (Section 1.3). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In

addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. The Fridericia correction method for calculating QTc will be used.

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, bradyarrhythmia's, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Please refer to the lenvatinib IB. 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.

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

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 participants 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

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. 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 Laboratory Manual. 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.

8.3.6.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours for urine or 72 hours for serum of the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Additional pregnancy testing must be performed on D1 of each cycle and within 24 hours prior to each TACE procedure.

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted every cycle during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception as per SoA (Section 1.3) and 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 study.

8.3.7 Performance Assessments

8.3.7.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 9) at screening, prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

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

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. Investigators need to document if an AE and/or SAE is associated with a medication error, misuse, or abuse.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

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

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

- All AEs from the time of treatment randomization through 90 days, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, must be reported by the investigator.

- All AEs meeting serious criteria, from the time of treatment randomization through 120 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of treatment randomization through 180 days following TACE, 120 days following pembrolizumab/IV placebo or 30 days following cessation of lenvatinib/oral placebo, whichever occurs last, must be reported by the investigator. If the participant initiates new anticancer therapy following discontinuation of study intervention, the time period for reporting pregnancies and exposure during breastfeeding is reduced to 30 days following cessation of study intervention.

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

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

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 8.

Table 8 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - hepatic ECIs except those considered due to disease progression as judged by the investigator	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - nonhepatic ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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 that the 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.

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

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

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

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

8.4.7 Events of Clinical Interest

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

Event 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 include any of the following events if the events are considered not due to disease progression or TACE as judged by the investigator. All of these events (if not associated with disease progression under study) will require holding study treatment, 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 6.6.3.

- 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)

8.5 Treatment of Overdose

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

- Pembrolizumab: ≥1000 mg
- Lenvatinib: any dose above the protocol-prescribed dose if associated with an adverse event

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

No specific information is available on the treatment of overdose of pembrolizumab or lenvatinib.

8.5.1 Reporting of Overdose

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

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

8.6 Pharmacokinetics

To evaluate the immunogenicity and pembrolizumab exposure in this indication, sample collections for analysis of ADA and PK are currently planned as shown in the SoA (Section 1.3). Blood samples for PK and ADA collected may be stored only at this time. Further analysis may be performed if required and reported separately if conducted. If

ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

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.

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Laboratory Manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

8.8.1 Planned Genetic Analysis Sample Collection

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8.9 Medical Resource Utilization and Health Economics

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

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

- All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation/randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.10 Visit Requirements

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

8.10.1 Screening

Within 28 days of treatment randomization, 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 prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. Exceptions are hepatitis, AFP, and thyroid testing which may be performed up to 28 days prior to the first dose of study intervention.

- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.

- For WOCBP, a urine or serum pregnancy test will be performed within 24 hours for urine or 72 hours for serum prior to 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 enrollment, 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 Visits

8.10.3.1 Safety Follow-up Visits

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 the EOI 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 EOI visit and the 30-day Safety Follow-up Visit should be performed at the EOI. EOI is defined as the date when the participant discontinues all study interventions.

For participants continuing with Efficacy Follow-up at ≥Q9W, if their 90-day Safety Follow-up Visit falls within the same window as their Efficacy 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 Efficacy Follow-up at ≥Q9W.

8.10.3.2 Efficacy Follow-up Visits

All participants who complete 2 years of study intervention or who discontinue study intervention prior to disease progression will continue to undergo tumor assessments Q9W in the Efficacy Follow-up Phase until disease progression is documented and confirmed by BICR or a new anticancer therapy is initiated, unless the participant withdraws consent. Following the primary analysis for the study, tumor assessments should be performed Q9W or more frequently per local standard of care. If a clinic visit is not feasible, the participant may be contacted by telephone or email. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, or end of study, whichever occurs first. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

For participants who receive TACE and new anticancer therapy at any time posttreatment, collection of posttreatment TACE and new anticancer therapy data is mandatory. In addition, disease progression from any cause after initiation of new anticancer therapy, including locoregional therapy and systemic therapy, will be reported.

8.10.3.3 Survival Follow-up

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

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

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

8.10.4 Survival Status

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in sSAP and referenced in the clinical study report for the study. Post hoc exploratory analyses will be clearly identified in the clinical study report. Other planned analyses (ie, those specific to the analysis of PK data or PROs) will be documented in a 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 Sections 9.2 through 9.12.

Study Design Overview	A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) with Pembrolizumab (MK-3475) in Combination with Transarterial Chemoembolization (TACE) Versus TACE in Participants with Incurable/Non-metastatic Hepatocellular Carcinoma (LEAP-012)
Treatment Assignment	Approximately 450 participants will be randomized in a 1:1 ratio between 2 treatment arms: • Arm A: Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally QD plus pembrolizumab 400 mg IV Q6W plus TACE • Arm B: Oral placebo QD plus IV placebo (normal saline) Q6W plus TACE. CCI [redacted]
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoints/Hypotheses	1) PFS per RECIST 1.1 assessed by BICR modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, with new intrahepatic lesions meeting LI-RADS 5 criteria. 2) OS
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing lenvatinib in combination with pembrolizumab plus TACE to placebo plus TACE on PFS and OS using the rerandomization tests based on the stratified log-rank test. Estimation of the HR will be performed using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

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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 will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The randomization according to the Pocock and Simon covariate-adaptive procedure will be implemented in an interactive voice response system.

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

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

9.4.1 Efficacy Endpoints

Primary

- **PFS** – according to RECIST 1.1 (adjusted to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ and incorporating a requirement that new intrahepatic lesions must meet LI-RADS 5 criteria) assessed by BICR: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first. See Section 9.6.1.1 for the definition of censoring.
- **OS**: the time from randomization to death due to any cause.

Secondary

- **ORR** – according to RECIST 1.1 assessed by BICR: a confirmed CR or PR.

- **DCR** – according to RECIST 1.1 assessed by BICR: CR, PR, or SD ≥6 weeks after randomization.

- **DOR** – according to RECIST 1.1 assessed by BICR: the time from first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first, in participants who show CR or PR. See Section 9.6.1.6 for the definition of censoring.

- **TTP** – according to RECIST 1.1 assessed by BICR: the time from randomization to the first documented disease progression. See Section 9.6.1.5 for definition of censoring.

- **PFS, OR, DC, DOR and TTP -** according to mRECIST assessed by BICR.

9.4.2 Safety Endpoints

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

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The analyses of efficacy endpoints other than DOR are based on the ITT population. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized. The DOR analysis will be based on the population of responders (participants that achieved CR or PR).

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study medication for 1 cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

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

9.5.3 PRO Analysis Populations

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

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

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

CCI [redacted] If there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, events, and responses in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP prior to the data base lock for the first IA and decisions regarding the pooling will be based on a blinded review of event and response counts by stratum.

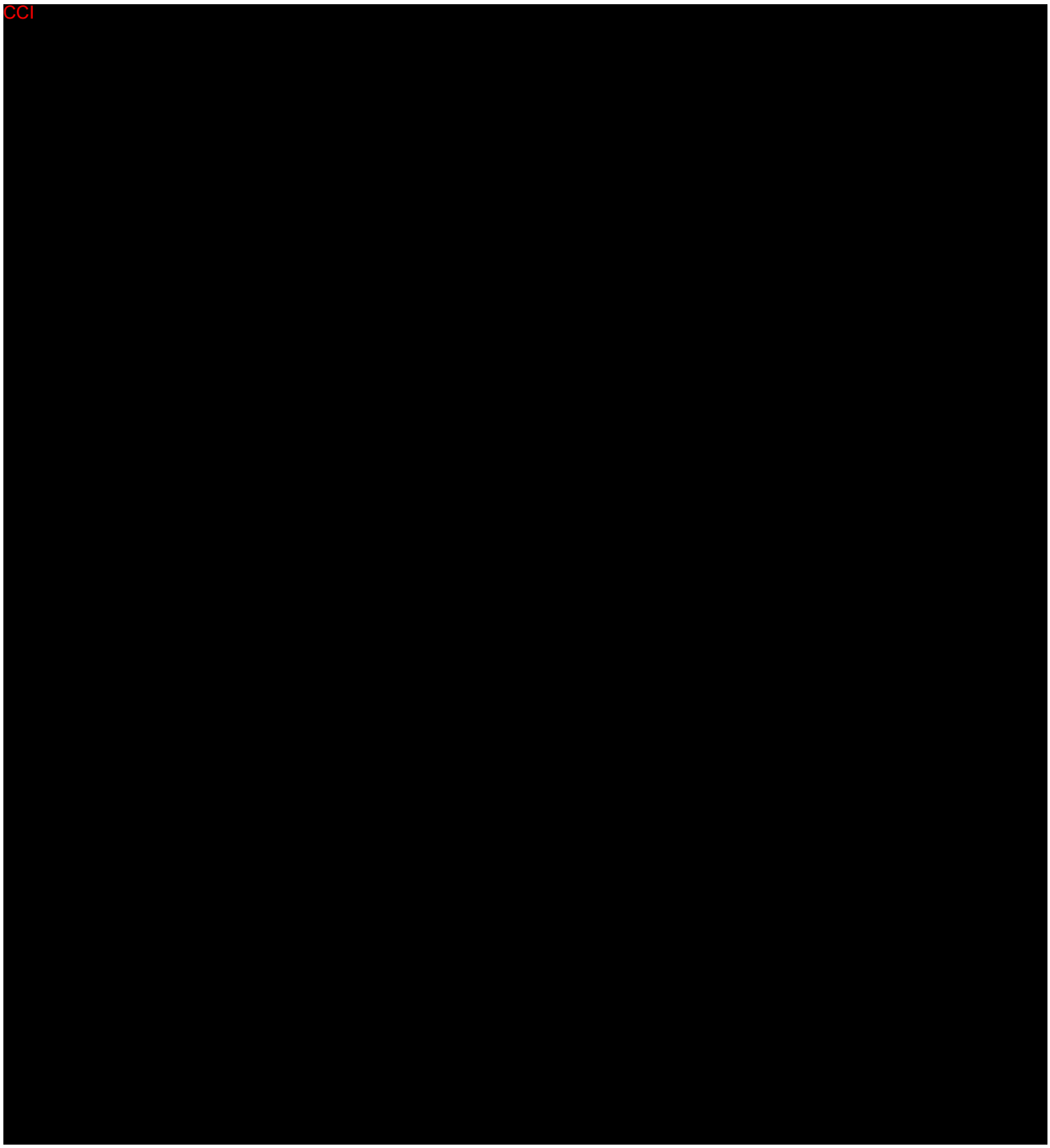
The hypothesis of treatment difference in PFS and OS will be tested by rerandomization test based on the stratified log-rank test. The stratified log-rank test will be performed as a sensitivity analysis. The rerandomization test will be performed by fixing the order of randomization of the study subjects, their covariates, and responses, and repeating the randomization procedure many times. For each instance of randomization, the stratified log-rank test will be performed. The p-value of the rerandomization test is equal to the fraction of randomizations with the value of the log-rank statistics as extreme or more extreme as the one obtained from the stratified log-rank test of the actual data.

9.6.1.1 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The hypothesis of treatment difference in PFS will be tested by a rerandomization test based on the stratified log-rank test. The stratified log-rank test will be performed as a sensitivity analysis. A stratified Cox proportional hazard model with Efron's

method of tie handling will be used to estimate the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported.

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Further details of sensitivity analyses will be described in sSAP as needed.

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9.6.1.2 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The hypothesis of treatment difference in survival will be tested by the rerandomization test based on the stratified log-rank test. The stratified log-rank test will be performed as a sensitivity analysis. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. Participants without documented death at the time of analysis will be censored on the date the participant was last known to be alive or the data cutoff, whichever is earlier.

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9.6.1.3 Objective Response

ORR, which is defined as the proportion of participants who have an OR, will be analyzed. The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] will be used for comparison of the objective response rates between 2 treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported.

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

9.6.1.4 Disease Control

DCR, which is defined as the proportion of participants who have a DC, will be analyzed. The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] will be used for comparison of the DC rates between 2 treatment groups. The difference in DCR and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported.

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

9.6.1.5 Time to Progression

The nonparametric Kaplan-Meier method will be used to estimate the TTP curve in each treatment group. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, HR) between 2 treatment groups. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported.

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. For the analysis, for the participants who have PD, 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 the BICR vendor, regardless of discontinuation of study intervention. Unlike the PFS analysis, death is not considered an event and does not impact the TTP censoring rules. Censoring rules for TTP are summarized in Table 10.

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9.6.1.6 Duration of Response

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed CR or PR will be included in this analysis. The nonparametric Kaplan-Meier method will be used to estimate the DOR curve in each treatment group; estimates and 95% CIs at specific duration time points will be provided. Censoring rules for DOR are summarized in Table 11.

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.



9.6.1.7 Analysis Strategy for Key Efficacy Variables

Table 12 summarizes the primary analysis approach for primary efficacy endpoints (PFS and OS). Sensitivity analysis methods are described above for each endpoint.

Analyses of the OR, DC, DOR, and TTP data will be performed at the time of the final OS analysis and/or at IAs that showed superiority in PFS or OS.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and IAs is described in Sections 9.7 and 9.8.

Table 12 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Hypothesis (H1)			
PFS per RECIST 1.1 by the BICR vendor modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ	Test: Rerandomization test based on the stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 9)
Primary Hypothesis (H2)			
OS	Test: Rerandomization test based on the stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date

BICR = blinded independent central review; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival.

[a] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors described in Section 9.6.1 will be applied to the analysis model.

9.6.2 Statistical Methods for Safety Analyses

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

9.6.2.1 Overall Safety Assessment

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

Point estimate and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided for AEs that occur in at least 10% of participants in any treatment group. The threshold of at least 10% of participants was chosen because the population enrolled in this study is in critical condition and usually experience various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, difference in the percentage of participants with specific Grade 3 to 5 AEs (≥5% of participants in one of

the treatment groups) and SAEs (≥5% of participants in one of the treatment groups) will also be summarized by point estimate and 95% CIs.

CIs for between treatment group differences will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences

Table 13 summarizes the analysis strategy for safety endpoints in this study.

Table 13 Analysis Strategy for Safety Parameters

Analysis Part	**Safety Endpoint**	**Descriptive Statistics**	**95% between-group CI (Graphical display)**
Overall Safety Assessment	Specific AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
	Specific Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Specific serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Any AE	X	
	Any Grade 3-5 AE	X	
	Any serious AE	X	
	Any drug-related AE	X	
	Any serious and drug-related AE	X	
	Any Grade 3-5 and drug-related AE	X	
	Discontinuation study treatment due to AE	X	
	AE that resulted in death	X	
	AE that led to dose interruption	X	
	AE that led to dose reduction	X	
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)	X	
	Change from Baseline Results (lab toxicity shift, vital signs)	X	
Assessment of safety topics of special interest	Pembrolizumab AEOSI	X	
AE = adverse event; AEOSI = adverse event of specific interest; CI = confidence interval; SOC = system organ class			

9.6.2.2 Assessment of Safety Topics of Special Interest

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

9.6.3 Statistical Methods for PRO Analyses

To evaluate the treatment effect on the health-related QoL outcomes at prespecified time points, a constrained longitudinal data analysis model will be applied, with the PRO score as the response variable, and the treatment by time interaction and stratification factors as covariates. The least squares mean change from baseline will be summarized. Group-wise comparisons will be performed, and the model-based least square mean score will be provided by treatment group and study visit.

Participants postbaseline EORTC QLQ-C30 scores will be classified as “improvement,” “stable,” or “deterioration” according to a predefined threshold (eg, 10-point or greater change from baseline). The number and proportion of participants with “improved”, “stable”, or “deteriorated” symptoms/scales will be summarized by treatment group.

TTD is defined as the time from the baseline PRO assessment to deterioration or death, whichever occurs first [Yang, J. C., et al 2013]. The Kaplan-Meier method will be used to estimate the times to deterioration survival curve for each treatment arm, and the Cox proportional hazards regression model will be used to estimate the magnitude of treatment difference.

Details of PRO analyses will be described in the sSAP.

9.6.4 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized and the primary reason for discontinuation will be displayed. Demographic variables (such as age, race, and ethnicity), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized. Baseline summaries will be based on eCRF data.

9.7 Interim Analyses

The eDMC will serve as the primary reviewer of the unblinded results of the efficacy and safety analyses and will make recommendations for discontinuation of the study or protocol

modification to an EOC (see Section 10.1.4.2) of the Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC and limited additional Sponsor personnel may be unblinded to results at the treatment level to act on these recommendations. The extent to which individuals are unblinded with respect to results of IAs will be documented by the internal team. Additional logistical details will be provided in the eDMC Charter.

9.7.1 Safety Interim Analyses

The eDMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the eDMC charter.

9.7.2 Efficacy Interim Analyses

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[redacted]

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[redacted]

CCI

[redacted]

9.8.3 Safety Analyses

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

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

The study will randomize 450 participants in a 1:1 ratio into the pembrolizumab plus lenvatinib or placebo plus lenvatinib arms. PFS and OS are primary endpoints for the study.

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9.10 Subgroup Analyses

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



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

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as number of cycles in which the participant receives the study intervention. Summary statistics will be provided on extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. 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.

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 fraud, scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee (SAC)

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

10.1.4.2 Executive Oversight Committee

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

10.1.4.3 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator

will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and

accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 17 will be performed by the local laboratory with the exception of hepatitis testing, which will be performed by the central laboratory. Local hepatitis testing is acceptable, including during the screening period. If hepatitis testing is performed locally, site should report hepatitis tests result in EDC prior to randomization.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 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. Refer to Appendix 7 for country-specific requirements.

- Pregnancy testing:

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

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

  - Pregnancy testing (urine or serum as required by local regulations) should be conducted during the intervention period and for at least 180 days post-TACE, 120 days post pembrolizumab/IV placebo or 30 days post lenvatinib/oral placebo, whichever occurs last.

  - 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 subject's participation in the study.

Table 17 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
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 (Tbil) and direct bilirubin (Dbil)[d]	Aspartate Aminotransferase (AST)/ Serum Glutamic Oxaloacetic Transaminase (SGOT)
	Alanine Aminotransferase (ALT)/ Serum Glutamic Pyruvic Transaminase (SGPT)	Alkaline phosphatase (ALP)	Magnesium	Phosphorus
	Amylase	Lipase[e]	Lactate Dehydrogenase	Triglycerides
	GGT			
Urinalysis/Urine dipstick testing	• Specific gravity • pH, glucose, protein, blood (or hemoglobin), ketones by dipstick[e]			
Other Tests	• Serology Anti-HCV (IgG), HCV viral load, HCV genotype, anti-HBs, HBsAg, Anti-HBc (total and IgM), and HBV viral load[f] • PT/INR • AFP • Serum or urine Pregnancy test • Thyroid-Stimulating Hormone (TSH)[g], Free thyroxine (FT4)[g], Triiodothyronine (T3)[g] • Serology HIV antibody as required by local health authority or institutional regulations. Refer to Appendix 10.7 for country-specific information.			

AFP = alpha fetoprotein; Anti-HBc = antihepatitis B core antibody; Anti-HBs = antihepatitis B surface antibody; GGT = gamma-glutamyl transferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgM = immunoglobulin M; INR = international normalized ratio; PT = prothrombin time; RBC = red blood cells; Tbil = total bilirubin; 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 Tbil is above ULN.

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

f All study-required laboratory assessments will be performed by a local laboratory, with the exception of hepatitis testing (Anti-HCV [IgG], HCV viral load, HCV genotype, anti-HBs, hepatitis B surface antigen [HBsAg], Anti-HBc [total and IgM], HBV viral load), which will be performed centrally. Local hepatitis testing is acceptable, including during screening period. If hepatitis testing is performed locally, site should report hepatitis test results in EDC prior to randomization.

g Free T4, T3, and TSH levels will be performed as indicated in Section 1.3 (Schedule of Activities). 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 prior to scheduled dosing. After Cycle 1, review of thyroid function test results after dosing is acceptable.

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 participant.

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

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

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

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

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." Lenvatinib overdose without an associated 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.4 Additional Events Reported

Additional events that require reporting in the same manner as SAE

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. 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 Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

  - If yes, did the AE resolve or improve?

  - If yes, this is a positive dechallenge.

  - If no, this is a negative dechallenge.

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

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

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

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

- Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
- No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure 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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not Applicable

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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 study enrollment.

10.5.2 Contraception Requirements

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

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

Not applicable

Confidential

085C4R4

10.7 Appendix 7: Country-specific Requirements

10.7.1 Germany

Section 1.3 Schedule of Activities

Study Period	**Screening[a]**	**Treatment Period**										**EOI**	**Notes**
		21-Day Cycles							**42-Day Cycles**				
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**		
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Frequency of cycles is Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond**
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	
HIV	X												Testing is required
a. All screening procedures should be performed within 28 days of allocation, unless otherwise noted.													

Section 1.1 Synopsis

Section 4.4 Beginning and End of Study Definition

Section 5.1 Inclusion Criteria

Section 7.1 Discontinuation of Study Intervention

Section 7.2 Participant Withdrawal from the Study

Section 8.1.1 Informed Consent

Section 8.1.1.1 General Informed Consent

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

All the references to a participant's "legally acceptable representative (or the participant's legally authorized representative)" in the protocol are not applicable for participants in Germany. This is because participants of legal age, who are not capable of comprehending the nature, significance and implications of the clinical trial and of determining their will, are excluded from participating in the clinical trial at German sites.

Section 1.3 Schedule of Activities

Section 5.2 Exclusion Criteria

Section 8.3.4 Echocardiogram or Multiple Gated Acquisition Scan

Only ECHO scans will be performed at the German sites for LVEF assessment in accordance with the institution's standard practice as MUGA scans are not a standard practice and are not notified to the Federal Office for Radiation Protection (BfS). Therefore, no MUGA scans will be performed in Germany.

Section 5.2 Exclusion Criteria

28 Participant has a known history of HIV infection. Testing for HIV is required at screening.

Appendix 2 Clinical Laboratory Tests

Other Screening Tests: Serology (HIV antibody).

10.7.2 United Kingdom

Section 1.3 Schedule of Activities

Study Period	**Screening[a]**	**Treatment Period**										**EOI**	**Notes**
		21-Day Cycles							**42-Day Cycles**				
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**		
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Frequency of cycles is Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond**
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	
HIV	X												Testing is required
a. All screening procedures should be performed within 28 days of allocation, unless otherwise noted.													

Section 5.2 Exclusion Criteria

28. Participant has a known history of HIV infection. Testing for HIV is required at screening.

Section 6.5.2 Prohibited Concomitant Medications

Live vaccines while participating in the study, and within 90 days of the last dose of study intervention.

- Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).
- Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

Appendix 2 Clinical Laboratory Tests

Other Screening Tests: Serology (HIV antibody).

10.7.3 Portugal

Section 1.3 Schedule of Activities

Study Period	**Screening[a]**	**Treatment Period**										**EOI**	**Notes**
		21-Day Cycles							**42-Day Cycles**				
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**		
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Frequency of cycles is Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond**
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	
HIV	X												Testing is required
a. All screening procedures should be performed within 28 days of allocation, unless otherwise noted.													

Section 5.2 Exclusion Criteria

28. Participant has a known history of HIV infection. Testing for HIV is required at screening.

Appendix 2 Clinical Laboratory Tests

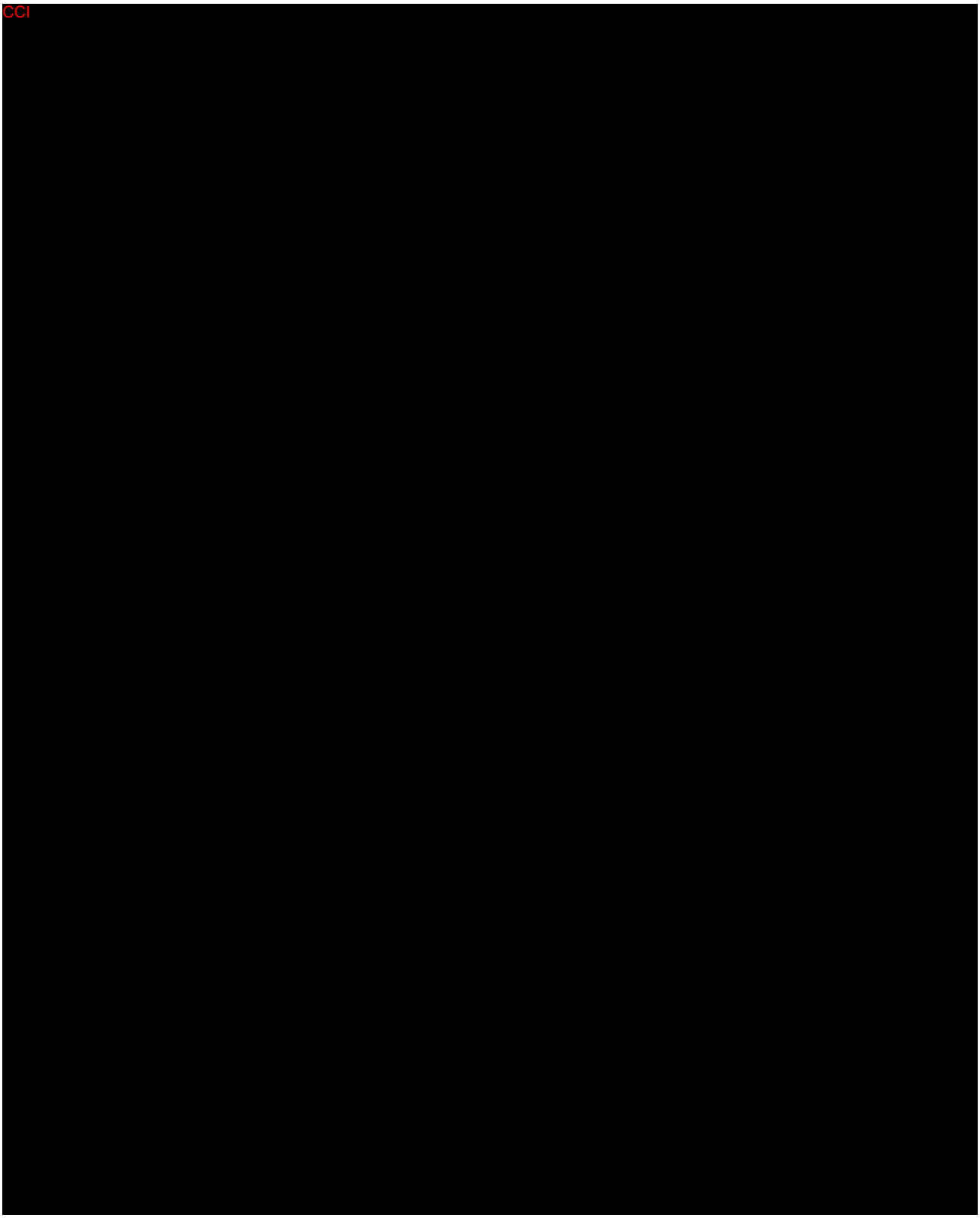
Other Screening Tests: Serology (HIV antibody).

10.7.4 South Korea

CCI



CCI



10.7.5 Ireland

Section 1.3 Schedule of Activities

Study Period	**Screening[a]**	**Treatment Period**										**EOI**	**Notes**
		21-Day Cycles							**42-Day Cycles**				
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**		
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Frequency of cycles is Q3W for Cycles 1 through 4 and Q6W for Cycles 5 and beyond**
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	
HIV	X												Testing is required
a. All screening procedures should be performed within 28 days of allocation, unless otherwise noted.													

Section 5.2 Exclusion Criteria

28. Participant has a known history of HIV infection. Testing for HIV is required at screening.

Appendix 2 Clinical Laboratory Tests

Other Screening Tests: Serology (HIV antibody).

10.7.6 Japan

Section 6.1 Study Intervention(s) Administered

Table 3 Study Interventions: Epirubicin and lipiodol used in this study for performing TACE are categorized as “product(s) used in the clinical study other than test product(s)” in Japan local regulation.

Intravenous solution, not provided by the Sponsor, as placebo for infusion in this protocol is not categorized as “product(s) used in the clinical study” in Japan local regulation.

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

Not applicable.

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10.9 Appendix 9: ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.[a]

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 perform work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to perform any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

[a] 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

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 surgery, 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 employs 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[a] (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[b,c] Or PT 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[d]	None	Grade I-II (mild or moderate)	Grade III-IV (severe or coma)

INR = International Normalized Ratio; PT = prothrombin time; ULN = upper limit of normal

[a] 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).

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

[c] For participants on anticoagulants (eg, Coumadin), only 1 point is assigned irrespective of the participant's INR and PT value.

[d] 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 semistupor, but responsive to verbal stimuli; Confusion; Gross disorientation
- Grade IV: Coma (unresponsive to verbal or noxious stimuli)

Interpretation:

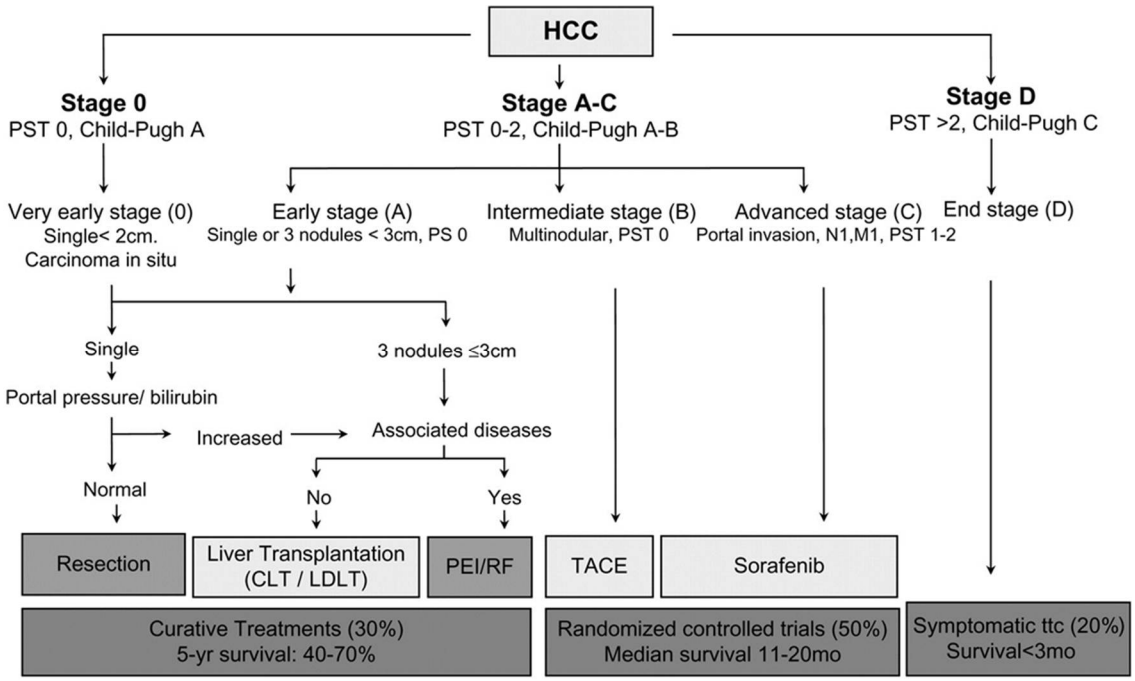
Chronic liver disease is classified into Child-Pugh Class A to C, employing the added score from above.

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

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

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

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

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 (see Table 18) Criteria for radiographic diagnosis of hepatocellular carcinoma using CT/MRI. Cirrhosis is required for radiographic diagnosis.

Table 18 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: Hepatoma Arterial-embolization Prognostic (HAP) Score

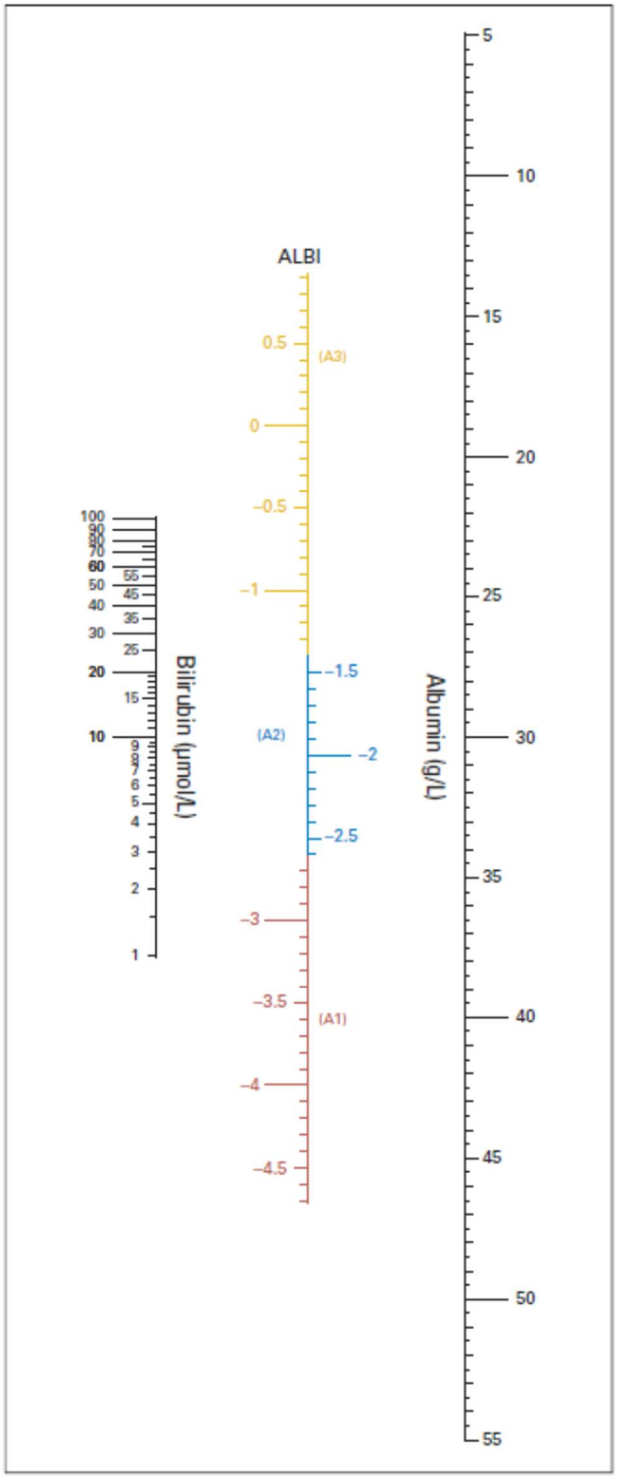
Participants are assigned one point for each of the following criteria [Kadalayil, L., et al 2013]:

- Albumin <3.6 g/dL
- Bilirubin >17 µmol/L (1 mg/dL)
- AFP >400 ng/mL
- Size of dominant tumor >7 cm

The sum of the points determines the HAP score as follows:

- HAP A: 0 points
- HAP B: 1 point
- HAP C: 2 points
- HAP D: 3 or 4 points

10.15 Appendix 15: ALBI Grade Nomogram



Source: [Johnson, P. J., et al 2015]

10.16 Appendix 16: Abbreviations

Abbreviation	Expanded Term
1L	first-line
2L	second line
AASLD	American Association for the Study of Liver Diseases
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AEOSI	Adverse event of special interest
AFP	alpha fetoprotein
ALBI	albumin- bilirubin (grade)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-HBc	Hepatitis B core antibody, total
Anti-HBc, IgM	Hepatitis B core antibody, IgM
Anti-HBe	Hepatitis B e antibody
Anti-HBs	Hepatitis B surface antibody
Anti-HCV	Hepatitis C antibody
Anti-HDV	Hepatitis D antibody
APaT	All-Participants-as-Treated
AST	Aspartate aminotransferase
AUC	area under the curve
BCG	*Bacillus* Calmette–Guérin
BCLC	Barcelona Clinic Liver Cancer
BICR	blinded independent central review
BMI	body mass index
BP	blood pressure
BSC	best standard of care
BW	body weight
C1D1	Cycle 1 Day 1
C4D1	Cycle 4 Day 1
CAC	Clinical Adjudication Committee
C_{avg}	average concentration over the dosing interval
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CL/F	apparent total clearance from plasma
C_{max}	peak concentration
C_{min}	trough concentrations
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CP	Child-Pugh
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CT	computed tomography
cTACE	conventional TACE
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4

Abbreviation	Expanded Term
CYP	cytochrome P-450
D Bili	direct bilirubin
DC	disease control
DCR	disease control rate
DDI	drug-drug interaction
DEB-TACE	drug-eluting bead TACE
DLTs	dose-limiting toxicities
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	Duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external data monitoring committee
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOI	end of intervention
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Lift Questionnaire – Core v 3.0
EORTC QLQ-HCC18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Hepatocellular Carcinoma Module
EOT	end of trial
ePROs	electronic patient-reported outcomes
EQ-5D	EuroQoL-5D
EQ-5D-5L	EuroQol-5-Dimension, 5-Level Questionnaire
ESMO	European Society for Medical Oncology
EU	European Union
FA	final analysis(es)
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
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GI	gastrointestinal
HAP	hepatoma arterial-embolization prognostic
HBc	antihepatitis B core antibody
HBeAg	Hepatitis B e antigen
HBs	antihepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HECI	Hepatic Events of Clinical Interest
HGRAC	Human Genetics Resources Administration of China
HIV	human immunodeficiency virus

Abbreviation	Expanded Term
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	Immunoglobulin G
IgG4	immunoglobulin G4
IgM	immunoglobulin M
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IO	immuno-oncology
IR	Interventional radiologist
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology (intervention allocation/randomization system)
ITT	Intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IWRS	integrated web response system
KIT	proto-oncogene c-Kit
KP-1	human pancreatic cancer cells
LAM	Lactational amenorrhea method
LI-RADS 5	Liver Imaging Reporting and Data System version 5
LVEF	Left ventricular ejection fraction
M&S	modeling and simulation
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
MUGA	Multigated acquisition
NAFLD	nonalcoholic fatty liver disease
NCI	National Cancer Institute
NDA	New Drug Application
NIMP/AxMP	noninvestigational/auxiliary medicinal product
NOAEL	no observed adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer

Abbreviation	Expanded Term
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	on-site formulation
OTC	over-the-counter
PD	progressive disease, disease progression
PD-1	programmed cell death 1
PDGFRα	platelet derived growth factor receptor alpha
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival after new poststudy anticancer therapy
Pgp	P glycoprotein
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PO	orally
PR	partial response
PRES/RPLS	Posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome
PRO	patient-reported outcome
PS	Performance Status
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
QD	once daily
QLG	Quality of Life Group
QOD	every other day
QoL	quality of life
QTc	corrected QT interval
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RET	ret proto-oncogene
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
RR	respiration rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIM	Site Imaging Manual
SoA	Schedule of Activities
SOP	Standard operating procedure
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Expanded Term
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
TACE	transarterial chemoembolization
TARE	transarterial radioembolization with Y90
TEAE	treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TMDD	target-mediated drug disposition
T-regs	regulatory T-cells
TSH	thyroid-stimulating hormone
TTD	time to deterioration
TTP	time to progression
UDS	urine drug screen
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US	United States
V	volume of distribution
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VEGFR1(FLT1)	VEGF high affinity binding receptor - tyrosine kinase FLT1
VEGFR2 (KDR)	also called a kinase domain receptor (KDR) or Flk-1, a VEGF receptor
VEGFR3 (FLT4)	fms-related tyrosine kinase 4, a VEGF receptor
WBC	white blood cell
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

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