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) in Combination with Pembrolizumab (MK-3475) Versus Lenvatinib in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma (LEAP-002)
NCT number:	NCT03713593
Document Date:	12-OCT-2022

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) in Combination with Pembrolizumab (MK-3475) Versus Lenvatinib in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma (LEAP-002)

Protocol Number: MK-7902-002-03 (E7080-G000-311)

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

Sponsor Name:

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

The study is cofunded by MSD and Eisai.

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	140284
EudraCT	2018-002983-26

Approval Date: 12 October 2022

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	12-OCT-2022	To space out clinic visits to every 6 weeks and imaging scans to every 12 weeks.
Amendment 2	14-APR-2021	To remove pharmacokinetic (PK) objective and update pembrolizumab dose modification table.
Amendment 1	14-MAY-2019	To address feedback from regulatory authorities and align with MK-7902 program standard updates.
Original Protocol	20-SEPT-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

To space out clinic visits to every 6 weeks and imaging scans to every 12 weeks.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Synopsis 1.3 Schedule of Activities (SoA) 8.1.8.1 Timing of Dose Administration 10.7.1 Germany 10.7.2 United Kingdom	Treatment cycles were lengthened from 21 days to 42 days.	The study scientific advisory committee recommended that switching from Q3W to Q6W visits for participants tolerating treatment would be clinically appropriate after the first 3 months of therapy. This decreases participant burden by reducing the number of site visits without compromising participant safety. Participants who require more frequent visits per investigator assessment will continue to be scheduled Q3W. This change is supported by published literature describing the safety of the pembrolizumab + lenvatinib combination [Makker, V., et al 2021].

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 4.1 Overall Design 8.10.3.2 Follow-up Visits	Imaging was changed from Q9W to Q12W.	Final analysis has now been completed for this study. Imaging window is being increased to every 12 weeks to be more in line with standard of care for subjects receiving lenvatinib monotherapy. All subjects have completed pembrolizumab/placebo treatment on this study.
1.3 Schedule of Activities	Note was added to indicate that home pregnancy testing should be conducted midcycle (Day 22).	Midcycle pregnancy tests were added because of the change from Q3W to Q6W visits.
8.3.7 Pregnancy Testing	This section was added to clarify pregnancy testing requirements and to add midcycle pregnancy tests.	Pregnancy testing information was clarified. Midcycle pregnancy tests were added because of the change from Q3W to Q6W visits.
8.4.5 Pregnancy and Exposure During Breastfeeding	Added information about reporting pregnancy complications.	To ensure accurate reporting of pregnancy events.
10.2 Appendix 2: Clinical Laboratory Tests	Removed details for pregnancy testing.	Details for pregnancy testing were added to Section 8.3.7.
8.3.6.2 Pregnancy Test	This section was removed.	The information that was in this section was redundant to that contained in Section 5.1 (Inclusion Criteria).

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	For Inclusion Criterion 9, the period of time for abstinence or contraception use after the last dose of lenvatinib was updated from 30 days to 7 days.	To align with current lenvatinib guidance.
5.2 Exclusion Criteria 6.5.2 Prohibited Concomitant Medications	Removed the use of factor X inhibitors as an exclusion criterion and from prohibited concomitant medications.	To align with other lenvatinib protocols. Anti-Xa inhibitors do not require INR monitoring, and may be used with lenvatinib treatment.
6.7 Intervention After the End of the Study	Language added to allow participants to be enrolled into an extension study (if available).	Participants will be allowed to enroll into an extension study (if available).
6.6.1.9 Management of Osteonecrosis of the Jaw	This section was added.	To comply with the lenvatinib label requirements for osteonecrosis of the jaw.
6.6.5 Other Allowed Dose Interruptions for Lenvatinib	Language added indicating lenvatinib dose interruptions for scheduled dental surgery or invasive dental procedures are allowed.	To comply with the lenvatinib label requirements for osteonecrosis of the jaw.
8.3.1 Physical Examinations	Included oral examination.	To comply with the lenvatinib label requirements for osteonecrosis of the jaw.

Section # and Name	Description of Change	Brief Rationale
6.6.1 Lenvatinib Dose Modification	Added cross-references to sections regarding management of gastrointestinal perforation and osteonecrosis of the jaw.	Added for completeness.
7.1 Discontinuation of Study Intervention	Removed unblinding as reason for discontinuation.	Participants are unblinded after final analysis.
8.1.10 Participant Blinding/Unblinding	Language added indicating participants may continue on study after unblinding of treatment assignment.	Participants are unblinded after final analysis, but may continue on study.
1.3 Schedule of Activities 8.8 Biomarkers	Removed serum biomarkers, plasma biomarkers, RNA, and stool collection from SoA.	Biomarker collections were streamlined to minimize burden to participants.
4.2.1.6 Planned Exploratory Biomarker Research	Removed text about stool samples. Removed references to pembrolizumab and immune-oncology.	Biomarker collections were streamlined to minimize burden to participants. To allow flexibility and current treatment options for exploratory biomarker research.
4.4 Beginning and End of Study Definition	Clarified definitions for beginning and end of study.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council.

Section # and Name	Description of Change	Brief Rationale
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events	Language added indicating investigators need to document SAE associated with medication error, misuse, or abuse.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council.
10.3 Definitions of Medication Error, Misuse, and Abuse	Definitions for medication error, misuse, and abuse were added.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council.
4.2.1.3 Patient-reported Outcomes	Added background information on patient-reported outcomes.	Added for completeness and clarity.
4.2.1.3.3 EQ-5D-5L	Section name was corrected.	The section heading was incorrect.
8.9 Medical Resource Utilization and Health Economics	The section name was modified.	To reduce redundancy.
1.3 Schedule of Activities 8.10.4 Vital Status	These sections were updated to use vital status (rather than survival status).	Revised for clarity.
8.2.1.4 RECIST 1.1 Assessment of Disease	Edited to delete unnecessary text.	To improve clarity.
10.1.4.1 Scientific Advisory Committee	This section was edited for clarity.	To clarify guidance.

Section # and Name	Description of Change	Brief Rationale
10.7.4 China	This section was updated to clarify China-specific biomarker collection, testing, and analysis.	Biomarker sample collection, testing, and analysis are dependent on approval by the Human Genetic Resources Administration of China.
10.7.5 Japan	Clarified study intervention classification in Japan.	Per PMDA regulation.

Table of Contents

DOCUMENT HISTORY **3**
PROTOCOL AMENDMENT SUMMARY OF CHANGES **4**
1 PROTOCOL SUMMARY **19**
1.1 Synopsis **19**
1.2 Schema **24**
1.3 Schedule of Activities (SoA) **25**
2 INTRODUCTION **37**
2.1 Study Rationale **37**
2.2 Background **37**
2.2.1 Pharmaceutical and Therapeutic Background 38
2.2.1.1 Lenvatinib 38
2.2.1.2 Pembrolizumab 38
2.2.1.3 Hepatocellular Carcinoma: Epidemiology and Current Therapeutic Options 39
2.2.1.4 Immunotherapy Interventions in HCC 41
2.2.1.5 Clinical Data on Lenvatinib and Pembrolizumab as Single Agents for the Treatment of HCC 41
2.2.1.6 Scientific Rationale for the Combination of Lenvatinib With Pembrolizumab 43
2.2.1.7 Clinical Data on Lenvatinib in Combination With Pembrolizumab for Treatment of Solid Tumors and HCC 43
2.2.2 Preclinical and Clinical Studies 44
2.2.3 Ongoing Clinical Studies 44
2.3 Benefit/Risk Assessment **44**
3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS **45**
4 STUDY DESIGN **47**
4.1 Overall Design **47**
4.2 Scientific Rationale for Study Design **48**
4.2.1 Rationale for Endpoints 48
4.2.1.1 Efficacy Endpoints 48
4.2.1.1.1 RECIST 1.1 49
4.2.1.1.2 iRECIST 49
4.2.1.1.3 Modified RECIST (mRECIST) 50
4.2.1.2 Safety Endpoints 50
4.2.1.3 Patient-reported Outcomes 50

4.2.1.3.1 EORTC QLQ-C30 51
4.2.1.3.2 EORTC QLQ- HCC18 51
4.2.1.3.3 EQ-5D-5L 51
4.2.1.4 Pharmacokinetic Endpoints 51
4.2.1.5 Pharmacodynamic Endpoints 51
4.2.1.6 Planned Exploratory Biomarker Research 51
4.2.1.7 Radiomic Biomarkers 53
4.2.2 Rationale for the Use of Comparator/Placebo 53
4.2.3 Rationale for Excluding Vp4 Patients 54
4.3 Justification for Dose 54
4.3.1 Lenvatinib 54
4.3.2 Pembrolizumab 55
4.3.3 Maximum Dose/Exposure for This Study 56
4.4 Beginning and End of Study Definition 56
4.4.1 Clinical Criteria for Early Study Termination 57
5 STUDY POPULATION 57
5.1 Inclusion Criteria 57
5.2 Exclusion Criteria 61
5.3 Lifestyle Considerations 64
5.3.1 Contraception 64
5.4 Screen Failures 64
5.5 Participant Replacement Strategy 65
6 STUDY INTERVENTION 65
6.1 Study Intervention(s) Administered 66
6.2 Preparation/Handling/Storage/Accountability 68
6.2.1 Dose Preparation 68
6.2.2 Handling, Storage, and Accountability 68
6.3 Measures to Minimize Bias: Randomization and Blinding 69
6.3.1 Intervention Assignment 69
6.3.2 Stratification 69
6.3.3 Blinding 69
6.4 Study Intervention Compliance 69
6.5 Concomitant Therapy 70
6.5.1 Allowed Concomitant Medication 70
6.5.2 Prohibited Concomitant Medications 70
6.5.3 Drug-Drug Interactions 72
6.5.4 Rescue Medications and Supportive Care 72
6.6 Dose Modification (Escalation/Titration/Other) 73

6.6.1 Lenvatinib Dose Modification 73
6.6.1.1 Management of Hypertension 75
6.6.1.2 Management of Proteinuria 77
6.6.1.3 Management of Diarrhea 78
6.6.1.4 Management of Thromboembolic Events 78
6.6.1.5 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome 79
6.6.1.6 Management of Hypocalcemia 79
6.6.1.7 Management of Hemorrhage 79
6.6.1.8 Management of Gastrointestinal Perforation or Fistula Formation 79
6.6.1.9 Management of Osteonecrosis of the Jaw 80
6.6.2 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue) 80
6.6.3 Guidance for Management of Hepatic Events of Clinical Interest 85
6.6.3.1 Management of HECI for Lenvatinib Toxicity: 87
6.6.3.2 Management of HECI for Pembrolizumab/Placebo: 87
6.6.4 Dose Modifications for Overlapping Toxicities 89
6.6.5 Other Allowed Dose Interruptions for Lenvatinib 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 91
7.1 Discontinuation of Study Intervention 91
7.2 Participant Withdrawal From the Study 92
7.3 Lost to Follow-up 92
8 STUDY ASSESSMENTS AND PROCEDURES 93
8.1 Administrative and General Procedures 93
8.1.1 Informed Consent 93
8.1.1.1 General Informed Consent 94
8.1.2 Inclusion/Exclusion Criteria 94
8.1.3 Participant Identification Card 94
8.1.4 Medical History 95
8.1.5 Prior and Concomitant Medications Review 95
8.1.5.1 Prior Medications 95
8.1.5.2 Concomitant Medications 95
8.1.6 Assignment of Screening Number 95
8.1.7 Assignment of Treatment/Randomization Number 95

8.1.8 Study Intervention Administration 96
8.1.8.1 Timing of Dose Administration 96
8.1.8.1.1 Lenvatinib 96
8.1.8.1.2 Pembrolizumab 96
8.1.9 Discontinuation and Withdrawal 96
8.1.10 Participant Blinding/Unblinding 97
8.1.11 Calibration of Equipment 97
8.2 Efficacy/Immunogenicity Assessments 98
8.2.1 Tumor Imaging and Assessment of Disease 98
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 iRECIST Assessment of Disease 100
8.2.1.6 Modified RECIST (mRECIST) Assessment of Disease 101
8.2.2 Patient-reported Outcomes 103
8.3 Safety Assessments 104
8.3.1 Physical Examinations 104
8.3.1.1 Full Physical Examination 104
8.3.1.2 Directed Physical Examination 104
8.3.2 Vital Signs 105
8.3.3 Electrocardiograms 105
8.3.4 Echocardiogram or Multiple Gated Acquisition Scan 105
8.3.5 Child-Pugh Score 106
8.3.6 Clinical Safety Laboratory Assessments 106
8.3.6.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis) 107
8.3.7 Pregnancy Testing 107
8.3.8 Performance Assessments 107
8.3.8.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale 107
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events 107
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 108
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events 110
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information 110
8.4.4 Regulatory Reporting Requirements for SAE 110

8.4.5 Pregnancy and Exposure During Breastfeeding 111
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs 111
8.4.7 Events of Clinical Interest (ECIs) 112
8.5 Treatment of Overdose 112
8.6 Pharmacokinetics 113
8.7 Pharmacodynamics 113
8.8 Biomarkers 113
8.8.1 Planned Genetic Analysis Sample Collection 113
8.9 Medical Resource Utilization and Health Economics 114
8.10 Visit Requirements 114
8.10.1 Screening 114
8.10.2 Treatment Period 115
8.10.3 Post-treatment Visit 115
8.10.3.1 Safety Follow-up Visit 115
8.10.3.2 Follow-up Visits 115
8.10.3.3 Survival Follow-up 115
8.10.4 Vital Status 116
9 STATISTICAL ANALYSIS PLAN 116
9.1 Statistical Analysis Plan Summary 116
9.2 Responsibility for Analyses/In-house Blinding 118
9.3 Hypotheses/Estimation 119
9.4 Analysis Endpoints 119
9.4.1 Efficacy Endpoints 119
9.4.2 Safety Endpoints 119
9.5 Analysis Populations 120
9.5.1 Efficacy Analysis Populations 120
9.5.2 Safety Analysis Populations 120
9.5.3 PRO Analysis Populations 120
9.6 Statistical Methods 120
9.6.1 Statistical Methods for Efficacy Analyses 120
9.6.1.1 Progression-free Survival 121
9.6.1.2 Overall Survival 122
9.6.1.3 Objective Response 122
9.6.1.4 Disease Control 123
9.6.1.5 Time to Progression 123
9.6.1.6 Duration of Response 123
9.6.2 Statistical Methods for Safety Analyses 125

9.6.3 Statistical Methods for PRO Analyses....127
9.6.4 Statistical Methods for Pharmacokinetics (PK) Analyses....127
9.6.5 Summaries of Baseline Characteristics and Demographics....127
9.7 Interim Analyses....128
9.7.1 Safety Interim Analyses....128
9.7.2 Efficacy Interim Analyses....128
9.8 Multiplicity....129
9.8.1 Progression-free Survival....130
9.8.2 Overall Survival....130
9.8.3 Objective Response....131
9.8.4 Safety Analyses....132
9.9 Sample Size and Power Calculations....132
9.9.1 Sample Size and Power for Efficacy Analyses....132
9.9.2 Sample Size and Power for Safety Analyses....133
9.10 Subgroup Analyses....133
9.11 Compliance (Medication Adherence)....134
9.12 Extent of Exposure....134
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS....135
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations....135
10.1.1 Code of Conduct for Clinical Trials....135
10.1.2 Financial Disclosure....137
10.1.3 Data Protection....137
10.1.3.1 Confidentiality of Data....138
10.1.3.2 Confidentiality of Participant Records....138
10.1.3.3 Confidentiality of IRB/IEC Information....138
10.1.4 Committees Structure....138
10.1.4.1 Scientific Advisory Committee....138
10.1.4.2 Executive Oversight Committee....138
10.1.4.3 External Data Monitoring Committee....139
10.1.5 Publication Policy....139
10.1.6 Compliance with Study Registration and Results Posting Requirements....139
10.1.7 Compliance with Law, Audit, and Debarment....140
10.1.8 Data Quality Assurance....140
10.1.9 Source Documents....141
10.1.10 Study and Site Closure....141
10.2 Appendix 2: Clinical Laboratory Tests....142

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 in the Same Manner as SAE....147
10.3.5 Recording AE and SAE....147
10.3.6 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor....151
10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting....152
10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing....153
10.5.1 Definitions....153
10.5.2 Contraception Requirements....154
10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research....155
10.7 Appendix 7: Country-specific Requirements....156
10.7.1 Germany....156
10.7.2 United Kingdom....156
10.7.3 France....157
10.7.4 China....157
10.7.5 Japan....158
10.8 Appendix 8: Hepatitis B Definitions and Treatment Considerations....159
10.9 Appendix 9: ECOG Performance Status....160
10.10 Appendix 10: Child-Pugh Score....161
10.11 Appendix 11: Barcelona Clinic Liver Cancer Staging System....163
10.12 Appendix 12: NYHA Criteria....164
10.13 Appendix 13: Clinical Studies Evaluating Drug-Drug Interactions With Lenvatinib....165
10.14 Appendix 14: Description of the iRECIST Process for Assessment of Disease Progression....166
10.15 Appendix 15: American Association for the Study of Liver Diseases (AASLD) Liver Imaging Reporting and Data System (LI-RADS) 5 Criteria....170
10.16 Appendix 16: Abbreviations....171
11 REFERENCES....174

LIST OF TABLES

Table 1 Study Schedule of Activities....25
Table 2 Adequate Organ Function Laboratory Values....60
Table 3 Study Interventions....66
Table 4 Dose Modification for Lenvatinib Treatment-Related Toxicity....73
Table 5 Dose Modification Guidelines for Lenvatinib-Related Adverse Events (for the Lenvatinib-Pembrolizumab Combination)....74
Table 6 Dose Modification and Toxicity Management Guidelines for Nonhepatic Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations....81
Table 7 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines....84
Table 8 Imaging and Treatment After First Radiologic Evidence of Progressive Disease....102
Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events....109
Table 10 Censoring Rules for Primary and Sensitivity Analyses of PFS....122
Table 11 Censoring Rules for TTP....123
Table 12 Censoring Rules for DOR....124
Table 13 Analysis Strategy for Key Efficacy Endpoints....125
Table 14 Analysis Strategy for Safety Parameters....127
Table 15 Summary of Interim and Final Analyses Strategy....128
Table 16 Efficacy Boundaries and Properties for Progression-free Survival Analyses....130
Table 17 Efficacy Boundaries and Properties for Overall Survival Analyses....131
Table 18 Possible Alpha-levels and Power for ORR Analysis....132
Table 19 Two-sided 95% CIs of Differences in Incidence of AE Rates Between the Two Treatment Groups for 375 Participants in Each Treatment Arm....133
Table 20 Protocol-required Safety Laboratory Assessments....142
Table 21 Hepatitis B Definitions and Treatment Considerations....159
Table 22 AASLD LI-RADS 5 Criteria....170

LIST OF FIGURES

Figure 1 Study Diagram 24
Figure 2 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator 103
Figure 3 Multiplicity Graph for Type I Error Control....129
Figure 4 Barcelona Clinic Liver Cancer Staging System....163

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) in Combination with Pembrolizumab (MK-3475) Versus Lenvatinib in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma (LEAP-002)

Short Title: Phase 3 Study of Lenvatinib (E7080/MK-7902) plus Pembrolizumab (MK-3475) for First-line Therapy of Advanced Hepatocellular Carcinoma

Acronym: LEAP-002

Hypotheses, Objectives, and Endpoints:

In first-line therapy of participants with advanced HCC following treatment with pembrolizumab plus lenvatinib versus treatment with placebo plus lenvatinib:

Primary Objectives	Primary Endpoints
- Objective: To compare progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 assessed by Blinded Independent Central Review (BICR) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. - Hypothesis (H1): Pembrolizumab plus lenvatinib is superior to placebo plus lenvatinib with respect to PFS per RECIST 1.1 assessed by BICR.	- PFS, defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
- Objective: To compare overall survival (OS). - Hypothesis (H2): Pembrolizumab plus lenvatinib is superior to placebo and lenvatinib with respect to OS.	- OS, defined as the time from randomization to death due to any cause.

Secondary Objectives	Secondary Endpoints
- Objective: To compare objective response rate (ORR) per RECIST 1.1 as assessed by BICR. - Hypothesis (H3): Pembrolizumab plus lenvatinib is superior to placebo plus lenvatinib with respect to OR per RECIST 1.1 assessed by BICR.	- Objective Response (OR): Complete response (CR) or partial response (PR).
- Objective: To evaluate duration of response (DOR), and disease control rate (DCR) per RECIST 1.1 as assessed by BICR.	- DOR, defined as 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. - Disease Control (DC), defined as a best overall response of CR, PR, or stable disease (SD). SD must be achieved at ≥6 weeks after randomization to be considered best overall response.
- Objective: To evaluate the safety and tolerability of pembrolizumab plus lenvatinib versus placebo plus lenvatinib.	- Adverse events (AEs), serious AEs (SAEs), immune-related (irAEs), and hepatic AEs. - Study intervention discontinuations due to AEs.
- Objective: To evaluate TTP per RECIST 1.1 assessed by BICR.	- TTP, defined as the time from randomization to the first documented disease progression.
- Objective: To evaluate efficacy outcomes per modified RECIST 1.1 (mRECIST) assessed by BICR.	- PFS, OR, DOR, DCR, and time to disease progression (TTP).

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

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	The treatment of participants with advanced hepatocellular carcinoma
Population	Participants with advanced hepatocellular carcinoma
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active
Study Blinding	Double-blind
Masking	Investigator Participant
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 44 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 750 participants will be randomized to 1:1 to 1 of 2 treatment arms.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
Arm A	Pembrolizumab	200 mg	Every 3 Weeks (Q3W)	Intravenous (IV) infusion	Day 1 of each 42-day cycle	Experimental
	Lenvatinib	12 mg (Body weight [BW] ≥60 kg) or 8 mg (BW <60 kg)*	Once Daily	Oral	Daily	Experimental
Arm B	Placebo	0 mg, 0.90% w/v NaCl	Q3W	IV infusion	Day 1 of each 42-day cycle	Placebo
	Lenvatinib	12 mg (BW ≥60 kg) or 8 mg (BW <60 kg)	Once Daily	Oral	Daily	Experimental

*Lenvatinib dosing is based on actual body weight at Screening and will be fixed for the duration of the study.
Abbreviations: BW=body weight; IV=intravenous; Q3W=every 3 weeks; w/v=weight/volume.

Total Number: 2 arms

Duration of Participation	Each participant will participate in the study from the time the participant signs the Informed Consent Form (ICF) 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 BICR. When clinically appropriate, participants can remain on study until confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), or unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab/placebo (approximately 2 years) whichever occurs first. Participants who attain an investigator-determined CR may consider stopping treatment with pembrolizumab/placebo after at least 24 weeks of study intervention have been administered. In addition, if a confirmed CR per RECIST 1.1 is attained, at least 2 additional doses of pembrolizumab/placebo must be received after CR is first documented. In the presence of clinical benefit, participants who complete 35 cycles of treatment with pembrolizumab/placebo (approximately 2 years) 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 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. When clinically appropriate, participants can remain on study until confirmed by the site per iRECIST, or initiating a non-study cancer treatment, withdrawing consent, or becoming lost 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. The end of the study will be the date of data cutoff for the final analysis or the time of last participant/last treatment, whichever occurs later.

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.	

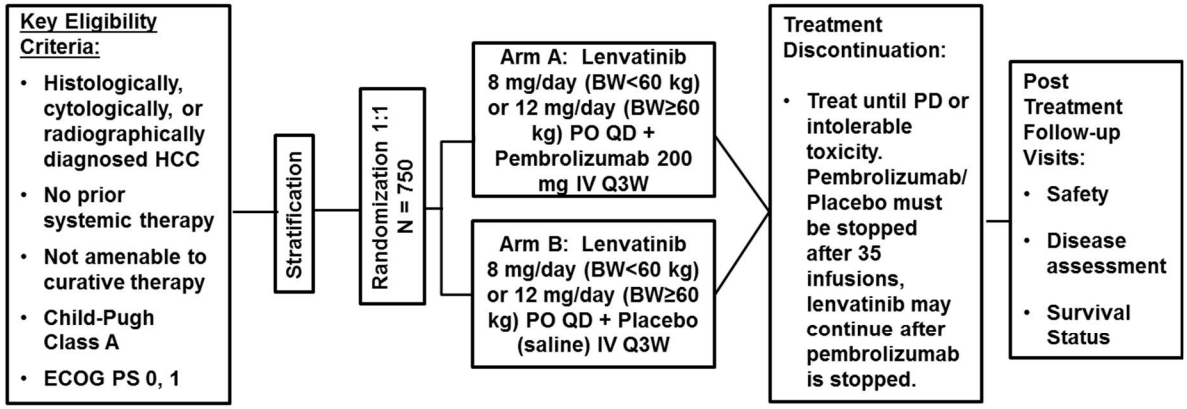
Study Accepts Healthy Volunteers: No

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



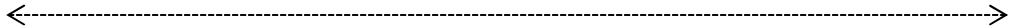
BW = body weight; ECOG PS = Eastern Cooperative Oncology Group performance status; HCC = hepatocellular carcinoma; IV = intravenous; Q3W = every 3 weeks; QD = once daily; PD = progressive disease; PO = per oral.

1.3 Schedule of Activities (SoA)

Table 1 Study Schedule of Activities

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
Administrative and General Procedures																
Informed consent	X															Consent form can be signed at any time prior to any protocol-specific screening procedures being performed. Additional consent is required at disease progression.
Inclusion/ exclusion	X															
Participant ID card	X															
Demographics	X															
Medical/ surgical history	X															
Prior/ concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
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. For participants that have been enrolled and randomized: The TEA is to be completed as soon as possible for those participants that have been previously randomized. For participants yet to be randomized: The TEA form must be completed prior to randomization. The investigator must provide the rationale for treatment choice prior to randomization.
Subsequent antineoplastic treatment													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 telephone or email.

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
Vital status																In participants who experience PD or start a new anticancer therapy, contact should be made (by telephone or visit) approximately every 12 weeks or more frequently, to assess for vital status. All subsequent antineoplastic therapy will be recorded. Updated vital status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their vital status (excluding participants who have a death event previously recorded).
Schedule of Study Intervention																
Lenvatinib Dispensing		X			X		X	X	X	X	X					Lenvatinib 12 mg (BW≥60 kg) or 8 mg (BW<60 kg) orally QD until PD or intolerable toxicity.
Pembrolizumab / placebo administration		X			X		X	X	X	X	X					Pembrolizumab 200 mg IV Q3W or normal saline placebo IV Q3W for 35 cycles.

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
Efficacy Procedures																
Tumor assessment – chest, abdomen, and pelvis (CT/MRI)[c]	X	<---------->										X		X		Historical scans performed within 28 days prior to randomization but before providing documented informed consent may be used if consistent with protocol requirements per BICR. All imaging visits have a scheduling window of within 7 days. Confirmation of all the following characteristics at screening is required prior to randomization: - Measurable disease per RECIST 1.1 by BICR - Radiographic diagnosis of HCC per ASSLD guidelines (Appendix 15) by Site, - Absence of VP4 portal vein thrombosis, inferior vena cava thrombosis, and cardiac involvement. Imaging must include triphasic CT/MRI for liver evaluation. Details to be provided in BICR SIM. Progression should be confirmed by BICR prior to discontinuing study treatment.

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
																For participants D/Cing for reasons other than BICR-confirmed PD, imaging should continue Q12W until BICR-confirmed PD. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.
Clinical Procedures or Assessments																
AE monitoring	X	X	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.
Full physical examination	X												X			To be performed within 7 days prior to start of study treatment.
Directed physical examination		X	X	X	X	X	X	X	X	X	X	X				
Child-Pugh Score	X															If any hepatic ECI criteria are met, document the Child-Pugh score with each visit until the hepatic ECIs resolve.
Vital signs (resting BP, pulse, RR, and temp) and weight	X	X	X	X	X	X	X	X	X	X	X	X	X			Additionally, participants with initial or recurrent systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored until systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg for 2 consecutive treatment cycles.

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
Height	X															
NYHA	X															See Appendix 12.
12-lead ECG	X	X			X		X	X	X	X	X		X			C1D1 and C2D1: predose and approximately 2 hr-post-lenvatinib dose assessments are required. Single 12-lead ECG. Participants must be in the recumbent position for 5 minutes prior to the ECG.
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 endoscopy	X															Gastroenterological upper endoscopy at Screening period is necessary only if more than 3 months have passed since the previous assessment.
ECOG performance status	X	X			X		X	X	X	X	X		X			To be assessed within 7 days prior to starting study intervention. Should be assessed prior to dosing at treatment visits.
Local Laboratory Procedures and Assessments[d]																
Pregnancy test (WOCBP only)	X				X		X	X	X	X	X	X	X	X		WOCBP require negative test prior to randomization. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. A serum or urine pregnancy test will be performed per Section 8.3.7. Home pregnancy testing should be conducted midcycle (Day 22 of each treatment cycle), while taking oral study intervention(s).

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
PT/INR	X				X		X	X	X	X	X	X	X			Screening samples collected within 7 days prior to first dose of study intervention.
CBC with Differential	X			X	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	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. For lab details see Section 10.2, Appendix 2.
Urine dipstick testing	X	X		X	X	X	X	X	X	X	X	X				Performed locally within 7 days prior to start of intervention. Testing to be performed on D1 of every cycle. D15 testing is mandatory in C1 and C2. 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.

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
T3/FT3, FT4, and TSH	X				X			X		X	X	X				Thyroid function tests will be assessed at Screening, followed by C2D1 and then every 2 cycles after that (ie, C4D1, C6D1, C8D1, etc.). Screening samples to be collected within 28 days prior to treatment initiation. After Cycle 1, participant will 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. Free T3 (FT3) is acceptable where T3 cannot be determined.
AFP	X							X			X*	X	X			Perform within 28 days prior to study treatment. *AFP every 9 weeks (Screening, C4, C7, C10, etc.) After Cycle 1, participant will be dosed even if AFP is not available prior to dosing; however, the results must be available and reviewed before the next scheduled visit.
HIV	X															Testing is not required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
Central Laboratory Assessments																
Anti-HCV (IgG)	X															Perform within 28 days prior to study treatment.
If Anti-HCV (IgG) positive:																If these conditions are met, the following test will be done 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[e]	X															
Anti-HBc (total and IgM), anti-HBs, HBV viral load, HBsAg[e]	X															

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
If (1) HBsAg+ and/or HBV viral load detectable or (2) anti-HBc+, anti-HBs-, HBsAg- and viral load <100 IU/mL																If these conditions are met, the following tests will be done within 28 days prior to study intervention.
Anti-HDV	X															
HDV RNA	X															
Anti-HBe and HBeAg[e]	X															
PK/Pharmacodynamic/Biomarker Assessment																
Pembrolizumab PK blood sample[f]		X			X						X					Predose C1D1, C2D1, C8D1.
Pembrolizumab ADA[f]		X			X						X					Predose C1D1, C2D1, C8D1.
Lenvatinib PK blood sample[f]		X		X	X											C1D1: 0.5-4 hr and 6-10 hr post dose; C1D15: predose and 2-12 hr postdose; C2D1: predose, 0.5-4 hr and 6-10 hr postdose Note: all predose samples should be collected within 2 hrs of lenvatinib dosing. Note: postdose samples not needed if lenvatinib administration is skipped.
Blood for genetic analysis[g]		X														Collect predose. See Section 8.8.1 for additional information.

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	
Blood for circulating tumor nucleic acids[g]		X			X		X		X		X	X				Collect predose C1D1, C2D1, C3D1, C5D1, and then D1 every 3 cycles thereafter (C8D1, C11D1, C14D1, etc.), and at EOT.
Tumor block or slides[g]	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	X	X*	X	X			Every effort should be made to administer PROs prior to drug administration, AE evaluation, and disease status notification. All PROs are to be performed at C1, C2, C3, C4, C5, C6, C7, C8, C9, and C10. *After C10 (Week 27), PROs are to be performed every 2 cycles (6 weeks) i.e. Cycle 12, 14, 16, 18. PROs are to be performed up to a year or EOT, whichever comes first, at D/C, and at the 30-day post-treatment discontinuation follow-up visit. A visit window of ±7 days will apply to PRO visit assessment. If the EOT visit occurs 30 days from the last dose of study treatment, a Safety Follow-up visit is not required; ePROs do not need to be repeated.

Study Period	**Screening**	**Treatment Period 42-Day Cycles**										**EOT**	**Post Treatment**			**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**					
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		**Safety FU[a,b]**	**Imaging FU[c]**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30 Days and 90 Days After Last Dose (+ 7)**	**Q12W (± 7)**	**Q12W (± 7)**	

Abbreviations: ADA = anti-drug antibody(ies); AE = adverse event; AFP = alpha fetaprotein; Anti-HBc = antihepatitis B core antibody, Total; Anti-HBe = antihepatitis B early antibody; Anti-HBs = antihepatitis B surface antibody; Anti-HDV = antihepatitis D antibody; BICR = blinded independent central review; BP = blood pressure; BW = body weight; 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; EORTC QLQ= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of treatment; ePRO = electronic patient-reported outcome; EQ-5D-5L = European Quality of Life 5-dimension, 5-level Questionnaire; FT3 = free triiodothyronine; FU = follow-up; HBeAg = hepatitis B early antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ID = identification; IgM = immunoglobulin M; INR = international normalized ratio; IRT = interactive response technology; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NYHA = New York Heart Association; PD = progressive disease; PE = physical examination; PK = pharmacokinetics; PRO = patient-reported outcome; PT = prothrombin time; Q3W = every 3 weeks; Q12W = every 12 weeks; QD = once daily; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; RNA = ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SIM = site imaging manual; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

a. If EOT visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up visit is not required. In this situation, all procedures required at both the EOT visit and the Safety Follow-up visit should be performed.
b. Safety FU will occur during 2 separate visits: 30 days AND 90 days after last dose. For participants continuing with imaging FU at ≥12W, 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 ≥12W.
c. Following the primary analysis for the study: follow-up visits and tumor assessments should be performed Q12W or more frequently if required by local standard of care.
d. Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified. Procedures/assessments should be performed prior to administration of study intervention.
e. At screening, participants must have results within 28 days prior to first dose. In the case of hepatic ECIs, additional tests are to be performed as described in Section 6.6.3, Guidance for Management of Hepatic Events of Clinical Interest. All additional laboratory tests should be performed by a central laboratory, if possible.
f. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.
g. See Section 10.7.4 for China-Specific requirement for submitting biomarker samples, including tissue, blood, and stool.

2 INTRODUCTION

2.1 Study Rationale

Hepatocellular carcinoma (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 United States (US). Patients with advanced HCC represent a group with high unmet need with low survival rates, few effective therapeutic options, and poor health-related quality of life (HRQoL).

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

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 programmed cell death 1 (PD-1) inhibitor, pembrolizumab, in second-line (2L) HCC (KEYNOTE-224) were published [Zhu, A. X., et al 2018]. These results included an objective response rate (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.

Early data of the combination of lenvatinib and pembrolizumab in HCC also show encouraging initial data with respect to both safety and efficacy [Ikeda, M., et al 2018]. The current study will evaluate lenvatinib plus pembrolizumab or placebo in a 1L HCC setting. The demonstrated 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 participants with 1L advanced HCC.

2.2 Background

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

Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Lenvatinib is a potent multiple-receptor tyrosine kinase (RTK) inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR1 [FLT1], VEGFR2 [KDR], and VEGFR3 [FLT4]) in addition to other proangiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor (FGF) receptors 1-4, platelet-derived growth factor receptor α, KIT, and RET.

Refer to the respective Investigator's Brochures (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 preexisting 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 neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence

shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of cluster of differentiation (CD) 8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells correlates with improved prognosis and long-term survival in several solid malignancies, including ovarian, colorectal, and pancreatic cancer; HCC; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can also 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 immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–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 CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in 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 (EU) overall (and in Western Europe specifically), as well as in North and South America, is relatively low (<10/100,000) [Ferlay, J., et al 2015].

The predominant risk factors for HCC vary in high- and low-rate regions. In most high-rate countries, particularly Asia and Africa, chronic hepatitis B virus (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, hepatitis C virus (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, nonalcoholic fatty liver disease, 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]. SEER data from 2000-2011 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 advanced, unresectable disease. As HCC is resistant to most traditional chemotherapy agents, the median survival for patients with advanced disease is typically 6 to 9 months without therapy [Qin, S., et al 2013]. With improved treatment options for hepatitis C, 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 in the near future [Petrick, J. L., et al 2016].

In a large Phase 3 study of sorafenib versus placebo in 1L HCC in the Western population, sorafenib showed a median improvement of 2.8 months compared with placebo (10.7 months vs 7.9 months; hazard ratio [HR] 0.69; $p<0.001$), despite a low response rate of 2% [Llovet, Josep M., et al 2008]. The time to progression (TTP) was 5.5 months and OS was 10.7 months in the treatment arm, compared with 2.8 and 7.9 months in the placebo arm, respectively. The HR for OS was 0.69 (95% confidence interval [CI]: 0.55-0.87, $p<0.001$) [Llovet, Josep M., et al 2008].

In patients from the Asia-Pacific region taking sorafenib, the median improvement in OS compared with placebo was 2.3 months (6.5 months vs 4.2 months; HR 0.68; $p=0.014$), although OS was shorter in this study [Cheng, A.-L., et al 2009]. In parts of Asia, the FOLFOX regimen (folinic acid, 5 fluorouracil, and oxaliplatin) has also been approved, based on a randomized study comparing FOLFOX with doxorubicin [Qin, S., et al 2013]. In that study, there was a nonsignificant trend toward improved OS in the FOLFOX arm, with some imbalances in the populations favoring the FOLFOX arm.

Lenvatinib was approved in Japan, US, EU, and China for first-line treatment of unresectable HCC (see Sec 2.2.1.5 for additional information). Currently, regorafenib is the only globally approved 2L therapy following sorafenib treatment in patients with HCC based on a data

from a Phase 3 study [Bruix, J., et al 2017]. Recently, cabozantinib has demonstrated improved OS versus placebo in patients with advanced HCC who failed prior sorafenib treatment [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 alpha fetoprotein (AFP) levels ≥400 ng/mL [Zhu, A. X., et al 2018]. While these both have demonstrated improved survival, the benefits remain modest, with associated side effects; thus, continued investigation of additional agents for advanced HCC patients remains crucial.

2.2.1.4 Immunotherapy Interventions in HCC

As described above, HCC often develops in the setting of inflammation of various types. 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 that 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 partial responses (PRs) were seen, lasting for 3.6, 9.2, and 15.8 months. Stable disease (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 demonstrated an ORR by blinded independent committee review (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 maximum tolerated dose (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 and Pembrolizumab 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, nonsmall cell lung cancer (NSCLC), endometrial cancer, glioma, melanoma, and ovarian cancer [Kudo, M., et al 2018]and lenvatinib IB. Lenvatinib was approved by Japan (on 23-MAR-2018), FDA (on 15-AUG-2018), the EC (on 20-AUG-2018), and China (04-SEPT-2018) for first-line treatment of unresectable HCC based on results from the open-label Phase 3 clinical trial E7080-G000-304 (REFLECT) study. In data published from the REFLECT study, 954 patients with 1L HCC were randomly assigned to receive lenvatinib at 12 mg or 8 mg once daily (QD) depending on body weight (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 to sorafenib (13.6 months vs 12.3 months; HR: 0.92; 95% CI: 0.79–1.06). Lenvatinib treatment also showed improvements when compared to sorafenib treatment in the following: ORR (24.1% vs 9.2%), progression-free survival (PFS) (7.4 months vs 3.7 months), and median TTP (8.9 months vs 3.7 months). The most common any-grade adverse events (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%] vs 249 [52%]), but an increased frequency of hypertension (201 [42%]) vs 144 [30%]).

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 complete response (CR) (1%), 17 PRs (16%), 46 SD (44%), 34 progressive disease (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 aspartate aminotransferase (AST) concentration in 7 (7%), increased alanine aminotransferase (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.

2.2.1.6 Scientific Rationale for the Combination of Lenvatinib With Pembrolizumab

In preclinical models, lenvatinib decreased the tumor-associated macrophage (TAM) population, which is known as an immune regulator in the tumor microenvironment. By decreasing TAMs, expression levels of cytokines and immune-regulating receptors were changed to increase immune activation. 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-A001-111) to assess the safety and preliminary antitumor activity of the combination of lenvatinib plus pembrolizumab in participants with selected solid tumors is currently ongoing.

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

E7080-A001-111 is an open-label Phase 1b/2 study in participants with selected solid tumors (NSCLC, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma or melanoma [excluding uveal melanoma]), which is being conducted in the US. Phase 1b of this study determined the MTD and recommended Phase 2 dose as 20 mg lenvatinib QD in combination with 200 mg of pembrolizumab given IV every 3 weeks (Q3W). In Phase 2, participants are assigned by tumor type to up to 6 cohorts (10 or 20 evaluable participants per cohort) to receive the MTD to assess the safety and efficacy of the combination in the selected tumor types. This phase is ongoing.

Study E7080-J081-115 is being conducted for participants with selected solid tumors in Japan to confirm the tolerability and safety for combination regimen of lenvatinib plus pembrolizumab at the MTD determined in E7080-A001-111 (lenvatinib 20 mg QD and pembrolizumab 200 mg Q3W IV).

Data submitted to ASCO 2018 of a Phase 1b 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 (ASCO 2018) [Ikeda, M., et al 2018]. No dose-limiting toxicities (DLTs) were reported in Part 1. 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, 22-MAR-2018, 30 patients were enrolled (Part 1, n = 6;

Part 2, n = 24). There was a manageable safety profile for the combination and notable antitumor activity. The ORR, excluding unconfirmed responses, was 3 (50.0%) for Part 1 and 4 (20.0%) for Part 2 by modified Response Evaluation Criteria in Solid Tumors (mRECIST) as assessed by investigator. 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 ongoing 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 and pembrolizumab (alone and in combination), have shown promising efficacy in participants with HCC, and preliminary safety data of the combination of lenvatinib and pembrolizumab suggest toxicity is manageable. Given the limited treatment options for patients with advanced HCC, there is an unmet medical need for novel therapies in this setting. The existing data suggest that inhibiting angiogenesis in combination with PD-1 blockade is a promising therapeutic strategy, and the benefit:risk assessment for participants included in this study is considered to be favorable. No unexpected risks have been reported in HCC with other immune check point inhibitors other than transient elevations in ALT and AST. Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent form (ICF) documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

In first-line therapy of participants with advanced HCC following treatment with pembrolizumab plus lenvatinib versus treatment with placebo plus lenvatinib:

Objectives	Endpoints
Primary	
• Objective: To compare progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 assessed by Blinded Independent Central Review (BICR) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. • Hypothesis (H1): Pembrolizumab plus lenvatinib is superior to placebo plus lenvatinib with respect to PFS per RECIST 1.1 assessed by BICR.	• PFS, defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
• Objective: To compare overall survival (OS). • Hypothesis (H2): Pembrolizumab plus lenvatinib is superior to placebo and lenvatinib with respect to OS.	• OS, defined as the time from randomization to death due to any cause.
Secondary	
• Objective: To compare objective response rate (ORR) per RECIST 1.1 as assessed by BICR. • Hypothesis (H3): Pembrolizumab plus lenvatinib is superior to placebo plus lenvatinib with respect to OR per RECIST 1.1 assessed by BICR.	• Objective Response (OR): Complete response (CR) or partial response (PR).

Objectives	Endpoints
• Objective: To evaluate duration of response (DOR), and disease control rate (DCR) per RECIST 1.1 as assessed by BICR.	• DOR, defined as 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. • Disease Control (DC), defined as a best overall response of CR, PR, or stable disease (SD). SD must be achieved at ≥6 weeks after randomization to be considered best overall response.
• Objective: To evaluate the safety and tolerability of pembrolizumab plus lenvatinib versus placebo plus lenvatinib.	• Adverse events (AEs), serious AEs (SAEs), immune-related (irAEs), and hepatic AEs. • Study intervention discontinuations due to AEs.
• Objective: To evaluate TTP per RECIST 1.1 assessed by BICR.	• TTP, defined as the time from randomization to the first documented disease progression.
• Objective: To evaluate efficacy outcomes per modified RECIST 1.1 (mRECIST) assessed by BICR.	• PFS, OR, DOR, DCR, and time to disease progression (TTP).
Tertiary/Exploratory	
• Objective: To evaluate efficacy outcomes per RECIST 1.1 and RECIST 1.1 modified for immune-based therapeutics (iRECIST) as assessed by the investigator.	• PFS, OR, DOR, DCR, and TTP.
• Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of lenvatinib and pembrolizumab in all participants.	• Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

Objectives	Endpoints
• Objective: To evaluate 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 (EORTC) Quality of Life Questionnaire—Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire—HCC 18 (QLQ-HCC18).	• HRQoL will be assessed using the global score of the EORTC QLQ-C30 and EORTC QLQ-HCC18. • TTD evaluated for EORTC QLQ-C30 and EORTC QLQ-HCC18 global health status/QOL. Details will be provided in sSAP.
• Objective: To characterize health utilities using EuroQol-5-Dimension, 5-Level Questionnaire (EQ-5D-5L).	• HRQoL will be assessed using the EQ-5D-5L.
• Objective: To identify novel radiomic biomarkers (based on combinations of imaging features) that may be useful as pre-treatment predictors of response, early indicators of response, or correlates of molecular biomarkers, based on analysis of tumor assessment images from all participants.	• OR

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

4 STUDY DESIGN

4.1 Overall Design

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

This is a multicenter, randomized, active-controlled, parallel-group, double-blinded study of lenvatinib in combination with pembrolizumab (MK-3475) versus lenvatinib with placebo in first-line intervention in participants with advanced hepatocellular carcinoma. Approximately 750 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 once daily (QD) plus pembrolizumab 200 mg IV Q3W
- Arm B: Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally QD plus placebo (normal saline) IV Q3W

Lenvatinib dosing is based on actual body weight at Screening and will be fixed for the duration of the study. Pembrolizumab/placebo will be administered for up to 35 cycles. Lenvatinib will be administered until PD or unacceptable toxicity. 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 versus lenvatinib plus placebo. On-study imaging assessments will be performed every 12 weeks (Q12W) 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 progressive disease (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 by telephone or visit 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.

This study will use a group sequential design, using an independent, external Data Monitoring Committee (eDMC) to monitor safety and efficacy during the course of the study. There will be 2 planned interim analyses conducted: IA1, when approximately 335 OS events (63% of expected total OS events); and IA2, when approximately 452 OS events (85% of expected total OS events) have been observed (see Section 9.7). The final OS analysis will be conducted when approximately 532 OS events have been observed. There will be 2 PFS analyses conducted, the first at the time of the first OS interim analysis (IA1) and a final PFS analysis at the time of the second OS interim analysis (IA2). The results of the interim analyses will be reviewed by the eDMC, which will provide recommendations for the study in accordance with the eDMC charter and the SAP described in detail in Section 9.0 - Statistical Analysis Plan (SAP).

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The study includes dual primary efficacy endpoints: PFS per RECIST 1.1 as assessed by BICR, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ and OS.

Progression-free survival 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. Real time determination of site-determined radiologic progression as determined by central review will be communicated to the site.

The endpoint of OS is the standard for demonstrating superiority of antineoplastic therapy in clinical studies for HCC. PFS is being included as a dual 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) compare ORR per RECIST 1.1 assessed by BICR and 2) evaluate duration of response (DOR), and disease control rate (DCR) per RECIST 1.1 assessed by BICR. 3) TTP per RECIST 1.1 assessed by BICR will also be evaluated and 4) Evaluating PFS, ORR, DOR, DCR, and TTP per mRECIST assessed by BICR are secondary objectives.

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

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

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

Exploratory efficacy objectives of this study include evaluating PFS, OR, DOR, DCR, and TTP per 1) iRECIST (modified RECIST for immune-based therapeutics) assessed by investigator, and 2) RECIST 1.1 assessed by investigator.

4.2.1.1.1 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 (see Section 8.2.1.4). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.1.2 iRECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (see Section 8.2.1.5). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

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

4.2.1.1.3 Modified RECIST (mRECIST)

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

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of adverse events (AEs)/serious adverse events (SAEs); and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Patient-reported Outcomes

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

4.2.1.3.1 EORTC QLQ-C30

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

4.2.1.3.2 EORTC QLQ- HCC18

The EORTC QLQ-HCC18 is a disease-specific questionnaire developed and validated to address measurements specific to HCC [Blazeby, J. M., et al 2004]. It is one of multiple disease-specific modules developed by the EORTC QLG (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.

4.2.1.3.3 EQ-5D-5L

The EuroQoL-5D-5L (EQ-5D-5L) is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-level scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.4 Pharmacokinetic Endpoints

No pharmacokinetic endpoints will be evaluated in this study.

4.2.1.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.1.6 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and

generate information that may better guide single-agent and combination therapy with antineoplastic drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability) contributing towards the development/progression of cancer and/or driving response to therapy. Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Evaluation of molecular targets and signaling pathways including angiogenesis- or and growth factor related signaling pathways related to pembrolizumab and lenvatinib may also be explored. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with antitumor therapies. Specific gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass

spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other blood-derived biomarkers

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

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

Country-specific requirements are noted in Appendix 7.

4.2.1.7 Radiomic Biomarkers

Computed tomography (CT) images of tumors contain information that is not captured by traditional size measurements, including radiographic features related to density, texture, morphology, and higher-order pixel relationships. Analysis of these features, individually and in combination, is commonly referred to as "radiomics." Radiomic signatures (combinations of radiographic features) have shown promising preliminary results in a variety of tumor types as novel biomarkers that are prognostic, predictive (of response to therapy), or indicative of molecular phenotypes.

CT scans will be obtained using typical standard-of-care techniques. Additional reconstructions of the images will be collected to allow maximal flexibility in analysis. Scans may be analyzed using a variety of machine learning tools, including traditional radiomics with predefined feature sets and deep learning approaches in which features are discovered during model development in a data-driven fashion. The goal would be to discover radiomic biomarkers that correlate with survival, AEs, and molecular biomarkers.

4.2.2 Rationale for the Use of Comparator/Placebo

Participants will be randomized to receive IV pembrolizumab or placebo. Both treatment arms will receive lenvatinib. Cross over will not be allowed at time of documented disease progression.

The standard 1L therapy for HCC worldwide is sorafenib, which has shown a survival advantage compared to best supportive care, but with only a few months' benefit in OS compared with placebo in a Western population [Llovet, Josep M., et al 2008]. Sorafenib has a median PFS of approximately 6 months and a median OS of approximately 12 months. Sorafenib has significant toxicity, with approximately 40% of patients permanently discontinuing due to toxicity [Iavarone, M., et al 2011]. The most frequent drug-related

Grade 3-4 AEs are diarrhea (8%) and Grade 3-4 palmar-plantar erythrodysaesthesia (8%) [Llovet, Josep M., et al 2008].

Lenvatinib, another antiangiogenic multikinase inhibitor, has a similar mechanism of action as sorafenib. In addition, it shows noninferior OS and an improved response rate and PFS compared with sorafenib in the 1L treatment of HCC. When comparing the AE profiles, lenvatinib has a decreased frequency of palmar-plantar erythrodysaesthesia compared to sorafenib, but an increased frequency of hypertension. PD-1 inhibitors have shown durable responses in unselected HCC participants. In the Phase 2 study of pembrolizumab monotherapy in 2L HCC (KEYNOTE-224), the ORR is 16.3% [Zhu, A. X., et al 2018]. The anti-PD-1 antibody nivolumab received accelerated approval in the United States for treatment of 2L HCC. At the time of the study start, there are no therapeutic combinations yet approved for 1L treatment of HCC.

Lenvatinib has already been approved in the United States, the EU, Japan, and China and will likely become a standard of care in much of the world for 1L HCC. Given this, it is believed to be an appropriate comparator arm. A normal saline placebo for pembrolizumab is being used in this study to maintain the blinding.

4.2.3 Rationale for Excluding Vp4 Patients

Blockage or thrombosis of the main portal vein, or the portal vein branch contralateral to the primary involved lobe, is defined as Vp4. Patients with Vp4 constitute approximately 3% of the HCC patient population [Katagiri. S. 2014]). Vp4 patients have significantly increased rates of hepatic decompensation compared to other patients with lesser grades of tumor thrombosis [Kuo, Y. H., et al 2018]. The low prevalence and the high degree of morbidity and mortality may result in the uneven distribution of patients across the treatment and control cohorts, thereby biasing the data, as has happened with vascular invasion imbalance in other studies [Llovet, J. M., et al 2013]. Additionally, excluding Vp4 patients allows for comparability to previous and current pembrolizumab and lenvatinib therapeutic studies in HCC patients.

4.3 Justification for Dose

4.3.1 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 area under the curve (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 subjects 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 subjects with low body weight resulted in an increase in lenvatinib AUC. The median value and range of individual AUCs at steady state for subjects 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 subjects treated with either starting dose. These findings support the appropriateness of the lower starting dose of 8 mg for subjects with BW <60 kg.

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 Barcelona Clinic Liver Cancer (BCLC) Stage B (n=9) or C (n=21), Child-Pugh (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.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2

mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.3 Maximum Dose/Exposure for This Study

The maximum dose for lenvatinib is 12 mg/day. Lenvatinib will be continued until disease progression or unacceptable toxicity. The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W up to 2 years.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent.

The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

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

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

This is a study in 1L therapy of participants of at least 18 years with advanced HCC.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

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

- Radiologic confirmation of diagnosis is provided by the study site. Clinically confirmed diagnosis of HCC as per the American Association for the Study of Liver Diseases (AASLD) criteria (Appendix 15) , which requires:

    - Radiographically evident cirrhosis AND

    - A liver mass that shows arterial phase hyperenhancement on triphasic CT or MRI, AND EITHER:

        - Is ≥20 mm with either nonperipheral portal washout or an enhancing capsule

    OR

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

2. Have BCLC Stage C disease, or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach (see Appendix 11).

3. Have a Child-Pugh class A liver score within 7 days prior to first dose of study intervention (see Appendix 10).

4. Have a predicted life expectancy of >3 months.

5. Have at least one measurable HCC lesion based on RECIST 1.1 as confirmed by the BICR vendor.

Demographics

6. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 within 7 days prior to first dose of study intervention.

7. Participant is male or female.

8. Participant is ≥18 years of age, at the time of providing the documented informed consent.

Male Participants

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

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

OR

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

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

    - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

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

Female Participants

10. 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 woman of childbearing potential (WOCBP)

    OR

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

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

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

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

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

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

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

Additional Categories

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

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

    - Antiviral therapy for HBV must be given for at least 4 weeks and HBV viral load must be less than 100 IU/mL prior to first dose of study drug. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment.

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

14. Adequately controlled blood pressure (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.

15. Have 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 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 mg/dL OR direct bilirubin ≤ULN for participants with total bilirubin levels >2 mg/dL
AST (SGOT) and ALT (SGPT)	≤5 × ULN
Amylase and lipase	≤ 1.5 × ULN
Albumin[3]	>3.0 g/dL
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT)	≤2 OR ≤1.5xULN

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.

Country-specific requirements are noted in Appendix 7.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

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

2. Bleeding or thrombotic disorders or anticoagulants requiring therapeutic international normalized ratio (INR) monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin is permitted.

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

   Note: ascites detectable on imaging studies only are allowed.

4. Portal vein invasion (Vp4), inferior vena cava, or cardiac involvement of HCC based on imaging.

5. Has had clinically diagnosed hepatic encephalopathy in the last 6 months unresponsive to therapy within 3 days. Participants on rifaximin or lactulose during screening to control their hepatic encephalopathy are not allowed.

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

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

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

9. Clinically significant hemoptysis from any source or tumor bleeding within 2 weeks prior to the first dose of study drug.

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

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

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

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

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

Prior/Concomitant Therapy

14. Has received any systemic chemotherapy, including anti-VEGF therapy, or any systemic investigational anticancer agents for advanced/unresectable HCC.

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

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

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

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

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

18. 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, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

19. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks 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

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

21. 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.

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

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

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

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

26. 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.

27. Prolongation of corrected QT (QTc) interval to >480 ms (corrected by Fridericia Formula).

28. Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by multigated acquisition scan (MUGA) or echocardiogram (ECHO).

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

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

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

32. Has known active tuberculosis (Bacillus tuberculosis).

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 participants ability to cooperate with the requirements of the study.

Other Exclusions

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

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

Country-specific requirements are noted in Appendix 7.

5.3 Lifestyle Considerations

5.3.1 Contraception

Lenvatinib and pembrolizumab may have adverse effects on a fetus in utero. The participant should adhere to the protocol-specified contraception requirements. Refer to Appendix 5 for approved methods of contraception.

Based on its mechanism of action, lenvatinib can cause fetal harm when administered to a pregnant woman. Lenvatinib may also result in reduced fertility in females of reproductive potential and may result in damage to male reproductive tissues leading to reduced fertility of unknown duration. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits.

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

Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention 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 lenvatinib and pembrolizumab will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm A	Experi-mental	Lenvatinib	Drug	Capsule	4 mg	12 mg (BW ≥60 kg) or 8 mg (BW <60 kg)	Oral	Once daily	Test Product	IMP	Centrally by Sponsor or locally by the study site, subsidiary, or designee
Arm A	Experi-mental	Pembrolizumab	Drug	Vial	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle	Test Product	IMP	Centrally by Sponsor
Arm B	Active Compa-rator	Lenvatinib	Drug	Capsule	4 mg	12 mg (BW ≥60 kg) or 8 mg (BW <60 kg)	Oral	Once daily	Comparator	IMP	Centrally by Sponsor or locally by the study site, subsidiary, or designee

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm B	Active Compar-ator	Placebo	Drug	Vial	Normal Saline, 0.90% w/v	0 mg	IV Infusion	Day 1 of each cycle	Placebo	IMP	Provided locally by the study site, subsidiary, or designee

BW = body weight; EEA =European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; w/v = weight/volume.

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

All study interventions will be administered on an outpatient basis.

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 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.

Country-specific requirements are noted in Appendix 7.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab/placebo are provided in the Pharmacy Manual. Lenvatinib is a capsule for oral administration and does not require preparation.

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

investigator is responsible for ensuring that a local discard/destruction procedure is documented.

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to lenvatinib + pembrolizumab study intervention and lenvatinib + placebo study intervention, respectively.

6.3.2 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

- Geographic region (Region 1: Asia vs. Region 2: Japan and Western regions, such as EU, North America, etc.)
- Macroscopic portal vein invasion or extrahepatic spread or both (Yes vs. No)
- AFP: ≤400 ng/mL vs. >400 ng/mL
- ECOG PS: 0 vs. 1

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. 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 group assignments.

6.4 Study Intervention Compliance

Interruptions from the protocol specified intervention for >28 consecutive days (lenvatinib) or for >12 weeks (pembrolizumab or placebo) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication 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 Medication

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a single lesion on an exceptional case-by-case basis after consultation with the Sponsor if considered medically necessary by the treating physician, as long as the lesion is NOT a RECIST 1.1-defined target lesion and is NOT administered for tumor control. Pembrolizumab/placebo should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study intervention; however, lenvatinib can be continued per investigator discretion during the palliative radiation. The specifics of the radiation treatment, including the location, will be recorded on the case report form (CRF).

6.5.2 Prohibited Concomitant Medications

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

- Concurrent anticancer therapies such as chemotherapy, targeted therapies (eg, tyrosine kinase inhibitors), antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or lenvatinib
- Locoregional therapy
- Radiation therapy

  Note: Radiation for pain or palliation is acceptable (see Section 6.5.1).

- 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.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after 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, 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.

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, over-the-counter (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 90 days after the last dose of study intervention should be recorded. Concomitant medications administered 120 days after the last dose of study intervention should be recorded for SAEs and events of clinical interest (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 Treatment Phase of this study.

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

There are no prohibited therapies during the post-treatment Follow-up Phase.

Country-specific requirements are noted in Appendix 7.

6.5.3 Drug-Drug Interactions

A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate) were not altered in the presence of lenvatinib. No significant DDI is therefore expected between lenvatinib and other CYP3A4/Pgp substrates. Therefore, there are no DDI-related concomitant medication prohibitions or restrictions.

Nonclinical studies identify CYP3A4 as the important CYP isozyme responsible for human hepatic metabolism of lenvatinib. However, clinical studies conducted showed that coadministration of lenvatinib with either inducers or inhibitors of CYP3A4/P-glycoprotein (P gp) are not of clinical concern. The main metabolic pathways for lenvatinib in humans were identified as 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. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.2, Table 6 and Section 6.6.3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 6 in Section 6.6.2 and Guidance for Management of Hepatic Events of Clinical Interest in Section 6.6.3 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification (Escalation/Titration/Other)

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.

Adverse events will be graded using NCI CTCAE Version 4.0. 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.

The starting dose of lenvatinib is 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally QD. Dose reductions of lenvatinib occur in succession based on the previous dose level. Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg QD, and 4 mg every other day [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), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 6.6.1.5), hypocalcemia (Section 6.6.1.6), hemorrhage (Section 6.6.1.7), gastrointestinal perforation (Section 6.6.1.8), and osteonecrosis of the jaw (Section 6.6.1.9) 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)

Lenvatinib Dose Reduction and Interruption Instructions		
Dose adjustment for lenvatinib treatment-related toxicity is AFTER interruption and resolution of study intervention as detailed in the table below. Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QOD]).		
Nonhematologic Toxicities		
Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment[c]	No change
Intolerable Grade 2[c] or Grade 3[d,e,h]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 more dose level
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discontinue lenvatinib
Grade 4[g,h]: Discontinue Lenvatinib		

Hematologic Toxicities and Proteinuria		
Treatment-Related Toxicity[a]	**Management**	**Dose Adjustment**
Grade 1 or Grade 2[e]		
	Continue treatment[c]	No change
Grade 3[e, i]		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	No change
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 dose level
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence [f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fifth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discontinue lenvatinib

Lenvatinib Dose Reduction and Interruption Instructions

Dose adjustment for lenvatinib treatment-related toxicity is AFTER interruption and resolution of study intervention as detailed in the table below. Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QOD]).

Grade 4[j]		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discontinue lenvatinib

Note: Grading according to CTCAE v4.0.
AE = adverse event; BMI = body mass index; CTCAE v4.0 = Common Terminology Criteria for Adverse Events Version 4.03; QD = once daily.

a An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) will require Sponsor's approval before treatment can be resumed. During treatment interruption, repeat AEs assessment at least every 7 days (until restarting administration).

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

c Grade 2 toxicities will be determined to be tolerable or intolerable by both the participant and investigator. If Grade 2 toxicity is determined to be intolerable, the dose of study drug will be reduced with or without dose interruption. Interruption for Grade 3 toxicities is mandatory.

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 treatment at a lower dose once their weight loss remains stable for at least 1 week and they reach at least a BMI of 25. The new stable weight should be used for future dose reductions.

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

f Not applicable for participants who start at 8 mg QD.

g Excluding laboratory abnormalities judged to be nonlife-threatening, which should be managed as Grade 3.

h For asymptomatic Grade ≥3 elevations of amylase and lipase, Sponsor should be consulted to obtain permission to continue treatment.

i For a Grade 3 thromboembolic event, with the exception of portal vein thrombosis developed during treatment, permanently discontinue lenvatinib. See Section 6.6.1.4

j Applies to hematologic toxicities only.

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 participants enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before 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, Table 1). Hypertension will be graded using NCI CTCAE v4.0, based on BP measurements only (and not on the number of antihypertensive medications). If the participant's initial BP measurement is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

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

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

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume 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 as a tool to aid the participant in collecting blood pressure 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 2 BP assessments at least 30 minutes apart:

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

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

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

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

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

    - Additional dose reduction should be discussed with the Sponsor.

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

1. Institute appropriate medical management

2. Discontinue lenvatinib

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:

Detection and Confirmation

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

2. A 24-hour urine collection or an immediate spot urine protein-to-creatinine ratio (UPCR) test is required in the following situations:

    - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on lenvatinib.
    - 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 24 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

- Grading according to NCI CTCAE v4.0 will be based on the 24-hour urinary protein result if one has been obtained.

Management of 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.

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 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. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the

treating physician. If a thromboembolic event is confirmed, instructions contained in Table 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, lenvatinib must be discontinued.

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

6.6.1.5 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 v4.0, 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 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 or life-threatening fistula.

6.6.1.9 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgment of adequate resolution (See Section 6.6.5).

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

Dose Modification and Toxicity Management for Non-hepatic Immune-related AEs Associated with Pembrolizumab

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

Dose Modification and Toxicity Management Guidelines for Non-hepatic irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6.

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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 non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further treatment with pembrolizumab/placebo.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab/placebo 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 treatment with pembrolizumab/placebo.	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 v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab/Placebo

Pembrolizumab/placebo 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 pembrolizumab/placebo within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

Country-specific requirements are noted in Appendix 7.

6.6.3 Guidance for Management of Hepatic Events of Clinical Interest

Hepatic ECIs (HECIs) have been described in Section 8.4.7. All of these HECIs will require holding study intervention and notification of 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.

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, alkaline phosphatase, γ-glutamyl transpeptidase, INR, and complete blood count with differential
- Measure HCV RNA viral load (applies only for participants who have current active HCV infection or had infection in the past)
- HBV DNA, HBsAg, 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% to 2% 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 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 Dose Reduction and Interruption Instructions Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QOD]). Any dose reduction below 4 mg QOD must be discussed with the Sponsor. Once the dose has been reduced, it cannot be increased at a later date.		
Lenvatinib Induced HECI	**Management**	**Dose Adjustment**
First occurrence	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 dose level.
Second occurrence (same toxicity or new toxicity)	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 more dose level.
Third occurrence (same toxicity or new toxicity)[a]	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 more dose level.
Fourth occurrence (same toxicity or new toxicity)	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Discontinue lenvatinib.
[a] Not applicable for participants who start at 8 mg QD.		

6.6.3.2 Management of HECI for Pembrolizumab/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/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 2-3 weeks: • anti-HBe, HBe antigen, anti-HBs, and HBV DNA levels (if not detected at the onset of ECI) Restart pembrolizumab/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.

	Diagnosis	**Management**
Hepatitis C exacerbation in participants with HCV RNA positive	Rapid elevation of ALT to >5×ULN and/or >3x baseline	Interrupt pembrolizumab/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/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)	
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 reoccurs with rechallenge	Interrupt pembrolizumab/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/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/placebo intervention if:** a) Laboratory abnormalities do not resolve within 3 weeks b) Steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks c) Decompensation to CP-C status

	Diagnosis	Management
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 Ruled out alcohol use and hepatotoxic drugs including herbal and alternative medications	Restart pembrolizumab/placebo only if laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade **within 3 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.

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 drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (~28 hours), and pembrolizumab is dosed Q3W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

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

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

2. Severity of AE

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

6.6.5 Other Allowed Dose Interruptions for Lenvatinib

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

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.
- For scheduled dental surgery or invasive dental procedures, stop lenvatinib for at least 1 week before the procedure, then restart lenvatinib when deemed clinically appropriate.

6.7 Intervention After the End of the Study

Upon study completion, participants are to be discontinued and may be enrolled in an extension study using pembrolizumab in combination with lenvatinib, if available.

6.8 Clinical Supplies Disclosure

This study is blinded but supplies are provided 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 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 that, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Confirmed radiographic disease progression outlined in Section 8.2.1 (exception if the Sponsor approves treatment continuation)
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Discontinuation of pembrolizumab/placebo for recurrent Grade 2 pneumonitis
- Discontinuation of pembrolizumab/placebo may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab or matching placebo beyond the date when the initial CR was declared.

- Completion of 35 treatments (approximately 2 years) with pembrolizumab/placebo

  Note: The number of treatments is calculated starting with the first dose of pembrolizumab/placebo. In the presence of clinical benefit, participants who complete 35 cycles of treatment with lenvatinib + pembrolizumab/placebo (approximately 2 years) may continue to receive lenvatinib alone until disease progression or intolerable toxicity.

- Participant has any of the following nonoverdose hepatic ECIs:

  - ALT >20×ULN (confirmed within 1 week)
  - Drug-related total bilirubin >10 x ULN
  - CP score of >9 points if not improved to CP score <9 by intervention within 3 days
  - Hepatic encephalopathy not manageable by therapy within 3 days
  - Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related
  - If ascites is not manageable by intervention within 3 days

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

7.2 Participant Withdrawal From the Study

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

If a participant withdraws from the study, they will no longer receive study treatment 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 or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study File Binder (or equivalent).

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

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

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

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

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally

acceptable representative prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

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

The participant or his/her legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The 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 written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/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 hepatitis B or hepatitis C, information on past and /or present antiviral treatment will be collected.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur 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 allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

The investigator must provide the rationale for not using sorafenib prior to randomization.

Treatment Eligibility Assessment (TEA)

The TEA is included in the study to document investigator assessment of participant suitability for potential treatment and rationale. These data may be required to support reimbursement efforts.

8.1.8 Study Intervention Administration

Administration of pembrolizumab will be witnessed by the investigator and/or study staff. Lenvatinib may be administered at home except on Day 1 of Cycles 1 and 2. Please refer to Section 8.1.8.1 for further detail.

Study treatment should begin within 3 days of randomization.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Lenvatinib

Lenvatinib is provided as 4-mg capsules. Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) once daily will be taken orally with water (with or without food) at approximately the same time each day in each 42-day cycle. However, on Day 1 of Cycles 1 and 2, lenvatinib will be administered 0 to 4 hours after completion of pembrolizumab administration.

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

8.1.8.1.2 Pembrolizumab

Pembrolizumab/placebo will be administered as a 30-minute IV infusion on Day 1 of each 42-day cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes –5 min/+10 min).

After Cycle 1 Day 1, pembrolizumab/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.

When a participant withdraws from participation in the study, all applicable activities scheduled for the discontinuation visit (End of Treatment Visit) should be performed (at the

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

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 drug 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 treatment 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 has taken place, the principal 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 may be allowed to continue study intervention and 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 is 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 BICR vendor can be found in the site imaging manual (SIM). Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Triple phase imaging of the liver is required, as described in the SIM. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on 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 BICR. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be submitted to the central imaging vendor.

When the investigator identifies radiographic progression per RECIST 1.1, the BICR will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor (see Section 8.2.1.4 and Figure 2). Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the investigator considers the participant has progressed, but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the BICR.

8.2.1.1 Initial Tumor Imaging

The screening images must be submitted to the central imaging vendor for retrospective review.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the central imaging vendor.

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 vendor (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

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 central imaging vendor.

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

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

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks 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 if the investigator elects not to implement iRECIST.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks) 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 as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg,

discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Initial tumor imaging showing site-assessed PD should be submitted immediately for BICR verification of PD. The site will be notified if the BICR verifies PD using RECIST 1.1. Figure 2 illustrates the imaging flow involving verification of PD for clinically stable participants.

8.2.1.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 14. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

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

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 14, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered

following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section1.3 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 14, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 8 and illustrated as a flowchart in Figure 2.

8.2.1.6 Modified RECIST (mRECIST) Assessment of Disease

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

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

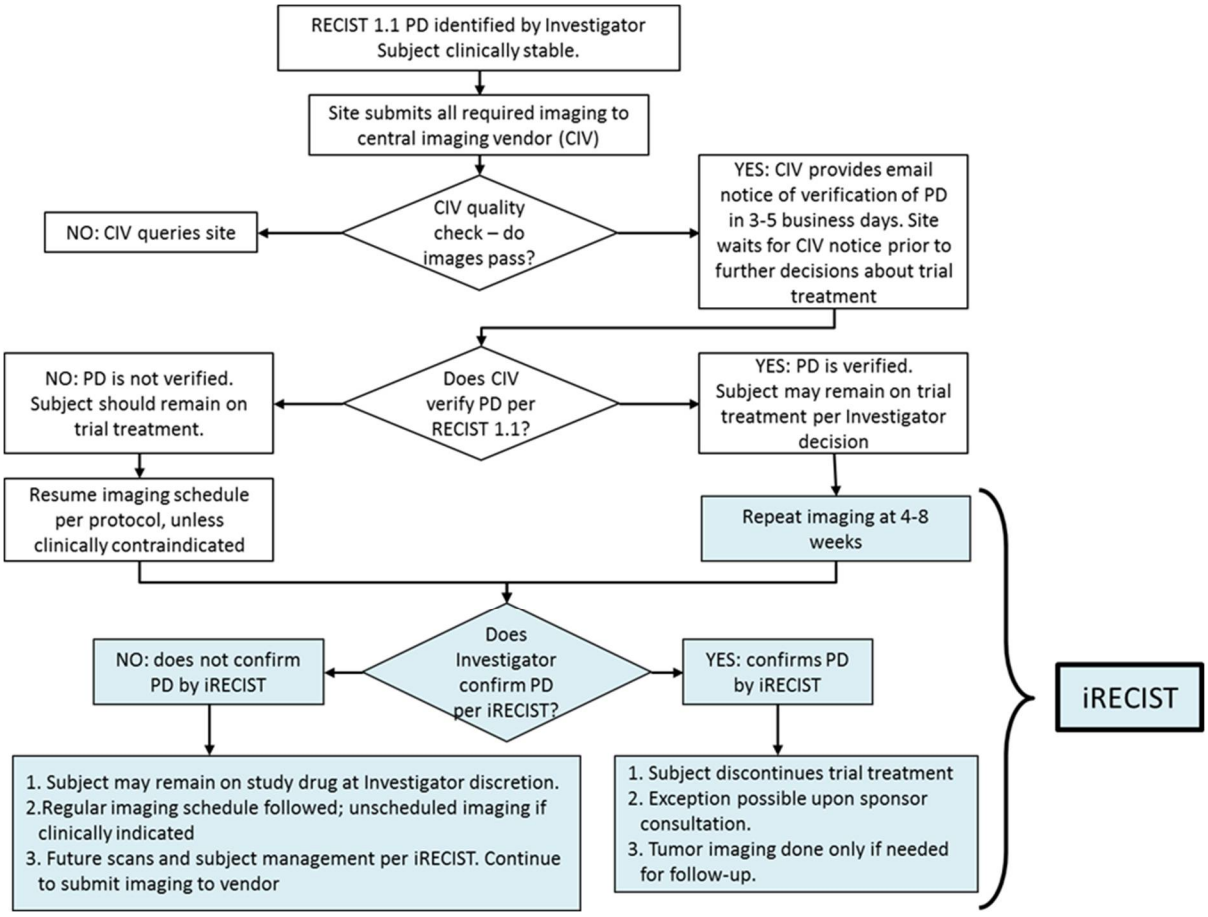
Table 8 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

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

Abbreviations: BICR=blinded independent central review; iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iPR=iRECIST partial response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.

Note: If progression has been centrally verified, further management is by the site, based on iRECIST. If pembrolizumab/placebo has been discontinued, iRECIST would not be applicable for lenvatinib alone. Any further imaging should still be submitted to the BICR vendor, but no rapid review will occur. If RECIST 1.1 disease progression has not been centrally verified, the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the BICR vendor with verification of progression request until RECIST 1.1 progression is verified by BICR.

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



CIV = central imaging vendor; iRECIST = RECIST 1.1 modified for immune-based therapeutics; PD = progressive disease RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

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: EORTC QLQ-C30, EORTC QLQ-HCC18, and then EQ-5D-5L. See SoA (Section 1.3) for ePRO administration schedule.

It is best practice and strongly recommended that electronic patient-reported outcomes (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 and/or EORTC QLQ-HCC18 questionnaires are not available for that language/country, and therefore cannot be completed by the participant at Cycle 1 Day 1, then the EORTC QLQ-C30 and/or EORTC QLQ-HCC18 will not be required

for this participant at any point during the study. The other study PRO measures must be completed as scheduled.

NOTE: For some sites, the translated EORTC QLQ-C30 and/or EORTC QLQ-HCC18 might become available after study startup and should be administered to participants at their time of enrollment; for some sites, the EORTC QLQ-C30 and/or EORTC QLQ-HCC18 translation might not be available for the entire duration of the study.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination (full physical or symptom-directed) including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

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

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examination are described in Section 1.3. Assessment for possible ascites and hepatic encephalopathy should be noted on every examination. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs. Height and weight will also be measured and recorded.

8.3.1.2 Directed Physical Examination

For cycles that do not required a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to the administration of the study intervention. Assessment for possible ascites and hepatic encephalopathy should be noted on every examination. New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

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

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

Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the participant's initial BP measurement is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BOP 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

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. Drugs known to prolong the QTc interval (including class Ia and III antiarrhythmics) must be used cautiously. Please refer to the 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 upon 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 patients with chronic liver disease and cirrhosis. The score considers 5 factors, 3 of which assess the synthetic function of the liver (ie, Tbili 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 case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 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 prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the study procedures 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.

8.3.7 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum) should be conducted at every protocol treatment cycle, as per SoA.
  - Home pregnancy testing should be conducted midcycle (Day 22 of each treatment cycle), while taking oral study intervention(s) as per SoA.
  - Pregnancy testing (urine or serum) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention(s) and should correspond with the time frame for the participant's contraception, as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is: as follows:
    - MK-3475: 120 days
    - Lenvatinib: 30 days
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.8 Performance Assessments

8.3.8.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 9) at screening (within 7 days of starting study intervention), 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 (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 4.

Progression of the cancer under study is not considered an AE as described in Section 8.4.7 and Appendix 4.

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

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

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

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

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

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

- All AEs from the time of treatment allocation/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 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, must be reported by the investigator.

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

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

Investigators are not obligated to actively seek AE or SAE 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 9.

Table 9 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	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Events of Clinical Interest	Report if -due to intervention -causes exclusion	Hepatic ECIs except those considered due to disease progression as judged by the investigator	Not required	Within 24 hours of learning of event

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	Timeframe to Report Event and Follow-up Information to SPONSOR:
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-hepatic ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
ECIs = events of clinical interest.				

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), 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. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

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

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

The Sponsor/designee will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

2. Hepatic ECIs include any of the following events if the events are considered not due to disease progression as judged by the investigator. All of these events (if not associated with disease progression under study) will require holding study 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 subjects with Baseline ALT <2×ULN: ALT ≥5×ULN
  - Among subjects 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

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose). An overdose of lenvatinib will be defined as any dose ≥20% over the prescribed dose described in the protocol.

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

8.6 Pharmacokinetics

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of antidrug antibodies (ADA) and PK are currently planned as shown in Section 1.3 (SoA). 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.

To evaluate the exposure of lenvatinib when coadministered with pembrolizumab blood samples will be collected as specified in the SoA (Section 1.3) from all participants. 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 operations/laboratory manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for genetic analysis
- Blood for circulating tumor nucleic acids analysis
- Tumor tissue

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

Country-specific requirements are noted in Appendix 7.

8.8.1 Planned Genetic Analysis Sample Collection

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites.

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 90 days following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.10 Visit Requirements

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

8.10.1 Screening

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

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study intervention 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 done 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 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 Post-treatment Visit

8.10.3.1 Safety Follow-up Visit

Safety Follow-up will occur during 2 separate visits: 30 days AND 90 days after last dose. One mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first. If End-of-treatment visit occurs ≥30 days from last dose of study treatment, the 30-day Safety Follow-up visit is not required. In this situation, all procedures required at both the End-of-treatment visit and the 30-day Safety Follow-up visit should be performed at the end-of-treatment visit. End of treatment is defined as the date when the participant discontinues all study interventions.

For participants continuing with imaging follow-up at ≥12W, if their 90-day Safety Follow-up Visit falls within the same window as their imaging follow-up visit, these visits may be combined. All procedures required at the Safety Follow-up Visit at 90 days will be performed at the imaging follow-up at ≥12W.

8.10.3.2 Follow-up Visits

Participants who discontinue study intervention for a reason other than disease progression will move into the Follow-up Phase and should be assessed Q12W to monitor disease status; if a clinic visit is not feasible, the participant may be contacted by telephone or email. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants will also be asked to complete HRQoL questionnaires as outlined in Section 8.2.2.

All participants who discontinue study intervention prior to disease progression will continue to undergo tumor assessments Q12W in the Follow-up Period 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 Q12W or more frequently per local standard of care.

8.10.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted by telephone or visit

approximately 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.

8.10.4 Vital Status

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, 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 International Conference on Harmonisation [ICH] Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the clinical study report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. 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) in Combination with Pembrolizumab (MK-3475) Versus Lenvatinib in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma (LEAP-002)
Treatment Assignment	Participants will be randomized in a 1:1 ratio to receive lenvatinib in combination with pembrolizumab or lenvatinib plus placebo (control arm). This is a double-blind study. Treatment allocation/randomization will be stratified according to the following factors: • Geographic region (Region 1: Asia vs. Region 2: Japan and Western regions, such as European Union (EU), North America, etc.) • Macroscopic portal vein invasion or Extrahepatic spread or both (Yes vs. No) • AFP: ≤400 ng/mL vs. >400 ng/mL • ECOG PS: 0 vs. 1
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT)

Primary Endpoints/Hypotheses	1) Progression-free Survival (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 2) Overall survival (OS)
Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses will be evaluated by comparing lenvatinib in combination with pembrolizumab to lenvatinib on PFS and OS using stratified log-rank tests. Estimation of the HR will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. Stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with weights proportional to the stratum size will be used for comparison of the objective response (OR) between the treatment arms.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% confidence intervals for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	Two efficacy interim analyses will be performed in this study. Results will be reviewed by an external Data Monitoring Committee. Details are provided in Section 9.7. First Interim Analysis (IA1) ◦ Timing: To be performed when approximately 335 OS events (63% of expected total OS events) are observed. With 21 months enrollment, the IA1 is expected approximately at Month 27, at which time approximately 474 PFS events are expected to have been accumulated. ◦ Purpose: The first interim efficacy analysis for both OS and PFS. Only if OS or PFS are significant, the analysis of the secondary endpoint of ORR (a single analysis) will also be performed. Second Interim Analysis (IA2) ◦ Timing: To be performed when approximately 452 OS events (85% of expected total OS events) have been observed, projected to occur at approximately Month 36, at which time approximately 571 PFS events are expected to have been accumulated. ◦ Purpose: the second efficacy IA for OS and final efficacy analysis for PFS. Final analysis ◦ Timing: When approximately 532 OS events have been observed, estimated to be 44 months after start of randomization. ◦ Purpose: Final efficacy analysis for OS.

Multiplicity	The multiplicity strategy in this study will be applied to the 2 primary hypotheses (superiority of lenvatinib in combination with pembrolizumab in OS and superiority of lenvatinib in combination with pembrolizumab in PFS) and the secondary hypothesis of superiority of lenvatinib in combination with pembrolizumab in OR. The overall Type I error across the 3 hypotheses above is strongly controlled at 2.5% (one-sided). The multiplicity strategy will follow the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] as described in Section 9.8, with initially 0.2% allocated to PFS hypotheses and 2.3% allocated to OS hypotheses. Within the PFS and OS hypotheses that are analyzed following a group sequential approach, the Type I error rates for the interim and final analyses will be controlled through the Lan-DeMets O'Brien-Fleming approximation alpha-spending functions specified for these endpoints as described in Section 9.8. The OR analysis does not use the group sequential approach. The secondary OR hypothesis is tested using only the OR data collected at the time of the first interim OS analysis, whenever the Type I error becomes available for the OR analysis.
Sample Size and Power	The sample size is approximately 750. The analysis of the OS endpoint is event driven. The testing of the OS hypothesis is conducted upon accumulating a preset number of events. The study is designed and will be conducted to accumulate approximately 532 OS events (unless superiority in OS is demonstrated at an interim analysis). For the primary endpoint OS, the study has approximately 90% power to demonstrate that pembrolizumab + lenvatinib is superior to lenvatinib at a one-sided 2.3% alpha level, if the underlying HR of OS is 0.75. For the primary endpoint PFS, the timing of the interim and final analysis will be driven by the accumulation of the OS events required for IA1 (interim PFS analysis) and IA2 (final PFS analysis). The study is anticipated to have approximately 92% power for the PFS hypothesis to demonstrate that lenvatinib in combination with pembrolizumab is superior to lenvatinib at a one-sided 0.2% alpha level, if the underlying HR of PFS is 0.70.

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 Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in an interactive voice response system.

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 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 in order to act on these recommendations. Additional logistical details will be provided in the eDMC Charter.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary

- **Progression-free survival (PFS) –** RECIST 1.1 assessed by BICR, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ: 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.

- **Overall Survival**: the time from randomization to death due to any cause.

Secondary

- **Objective Response (OR) –** RECIST 1.1 assessed by BICR: a confirmed CR or PR.

- **Duration of Response (DOR) –** 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 demonstrate CR or PR. See Section 9.6.1.6 for the definition of censoring.

- **Disease Control (DC)-RECIST 1.1 assessed by BICR:** CR, PR, or SD after ≥6 weeks.

- **Time to Progression (TTP)-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, DOR, DC, and TTP** – 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 intention-to-treat (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 complete or partial response).

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the All Participants as Treated (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 FAS population, defined as participants who have at least one PRO assessment available and have received at least one dose of study intervention.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary efficacy objectives. Methods related to exploratory objectives will be described in the sSAP. 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 will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity. The 4 stratification factors used for randomization, including geographic region (Region 1: Asia vs Region 2: Japan and Western regions), macroscopic portal vein invasion or extrahepatic spread or both (Yes vs. No), AFP (≤400 ng/mL vs >400 ng/mL), and ECOG PS (0 vs 1), will be applied to all stratified efficacy analyses, in particular, stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method

[Miettinen, O. and Nurminen, M. 1985]. If required, some of the small strata among the 16 strata formed by the 4 factors might be pooled for analyses in a meaningful way; the pooling strategy will be documented in the sSAP prior to the data base lock for the first interim analysis and used for all stratified analyses.

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 hypotheses of treatment difference in PFS will be tested by the stratified log-rank test. 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 Efron's method of tie handling and 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 primary 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 drug. Additional analyses will be performed for comparison of PFS per RECIST 1.1 and iRECIST by investigator assessment and PFS analysis for PD per mRECIST by the BICR vendor.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 via BICR modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ by the imaging vendor, 1 primary analysis and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are after more than 1 missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The first sensitivity analysis follows ITT principles. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers discontinuation of treatment or initiation of an anticancer treatment after discontinuation of study-specified treatments, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 10.

Table 10 Censoring Rules for Primary and Sensitivity Analyses of PFS

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

9.6.1.2 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The hypotheses of treatment difference in survival will be tested by the stratified log-rank test. 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.

9.6.1.3 Objective Response

The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with weights proportional to the stratum size will be used for comparison of the objective response rates between the treatment arms. A 95% CI for the difference in response rates between the treatment arms will be provided.

The ORR analysis will be conducted according to the hypotheses testing plan as described in Section 9.7 – Interim Analyses and Section 9.8 – Multiplicity.

9.6.1.4 Disease Control

The Stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with weights proportional to the stratum size will be used for comparison of the DC rates between the treatment arms. A 95% CI for the difference in response rates between the treatment arms will be provided.

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 the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported.

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 drug. Unlike the PFS analysis, death is not considered an event. Censoring rules for TTP are summarized in Table 11.

Table 11 Censoring Rules for TTP

Situation	Primary Analysis
Death only	Censored at date of randomization or date of last non-PD disease assessment, whichever is later
No PD and no death; new anticancer treatment is not initiated	Censored at last non-PD disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last non-PD disease assessment before new anticancer treatment
PD documented after ≤1 missed disease assessment	Progressed at date of documented PD
PD documented after ≥2 missed disease assessments	Censored at last disease assessment prior to the ≥2 consecutive missed disease assessments

PD = progressive disease; TTP = time to progression.

9.6.1.6 Duration of Response

Participants who achieved CR or PR and are alive, have not progressed, have not initiated new anticancer treatment, and have not been determined to be lost to follow-up are considered ongoing responders at the time of 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 12.

Table 12 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (nonevent)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (nonevent)
Death or progression after ≥2 consecutive missed disease assessments or after new anticancer therapy	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (nonevent)
Death or progression after ≤1 missed adequate disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)
DOR = duration of response; PD = progressive disease. Participants are considered to have an ongoing response if alive, have not progressed, have not started a new anticancer therapy, and have not been determined to be lost to follow-up.		

Table 13 summarizes the primary analysis approach for primary (PFS and OS) and key secondary (OR) efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

Analyses of the DC, TTP, and DOR data will be performed at the time of the interim and final analysis of OS.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 9.7 – Interim Analyses and in Section 9.8 – Multiplicity.

Table 13 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: 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 10)
Primary Hypothesis (H2)			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Secondary Hypothesis (H3)			
OR per RECIST 1.1 by the BICR vendor	Stratified M & N method[b]	ITT	Participants with missing response data are considered nonresponders

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

[a] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (see Section 6.3.2) will be applied to the analysis model.

[b] Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]

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.

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory, vital signs, and ECG parameters are either prespecified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or adverse events of special interest (AEOSI) that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. AEOSI that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination

of statistical significance is not expected to add value to the safety evaluation. Similarly, the combination of pembrolizumab and lenvatinib has not been associated with any new safety signals. Finally, there are no known AEs associated with participants with HCC for which determination of a *p* value is expected to impact the safety assessment. Therefore, there are no Tier 1 events expected in this study.

Tier 2 Events

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

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other adverse experiences and PDLCs will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 event because the population enrolled in this study are in critical conditions 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, Grade 3 to 5 AE (≥5% of participants in one of the treatment groups) and SAE (≥5% of participants in one of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not prespecified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AEs (≥10% of participants in one of the treatment groups)	X	X
	Any Grade 3 to 5 AE (≥5% of participants in one of the treatment groups)	X	X
	Any serious AE (≥5% of participants in one of the treatment groups)	X	X
Tier 3	Any AEs		X
	Discontinuation due to AE		X
	Change from baseline results (laboratory test toxicity grade)		X
AE = adverse event; CI = confidence interval; X = results will be provided. The rainforest plots including the treatment difference and its 95% CI will be applied for Tier2 AEs.			

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 (cLDA) model will be applied, with the PRO score as the response variable, and the treatment by time interaction and stratification factors as covariates. Least square mean (LS mean) change from baseline will be summarized. Groupwise comparisons will be performed and model-based LS mean score will be provided by treatment group and study visit.

Participants post-baseline EORTC QLQ-C30 scores will be classified as “improvement”, “stable”, or “deterioration” according to a predefined threshold (e.g. 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.

Time to deterioration 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 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 Statistical Methods for Pharmacokinetics (PK) Analyses

No pharmacokinetic endpoints will be evaluated in this study.

9.6.5 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant 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), 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.

9.7 Interim Analyses

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

Two interim efficacy analyses are planned in addition to the final analysis for this study. Results of the interim analyses will be reviewed by the eDMC. Details on the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 9.8.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 15.

Table 15 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	PFS OS OR (if Type I error available)	when approximately 335 OS events (63% of expected total OS events) are observed	~27 months	• Interim PFS and OS analyses ORR analysis if Type I error available
IA2	PFS OS	when approximately 452 OS events (85% of expected total OS events) have been observed	~36 months	• Final PFS and interim OS analyses
Final Analysis	PFS OS	when approximately 532 OS events have been observed	~44 months	• Final OS analysis
IA1 = interim analysis 1; IA2 = interim analysis 2; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.				

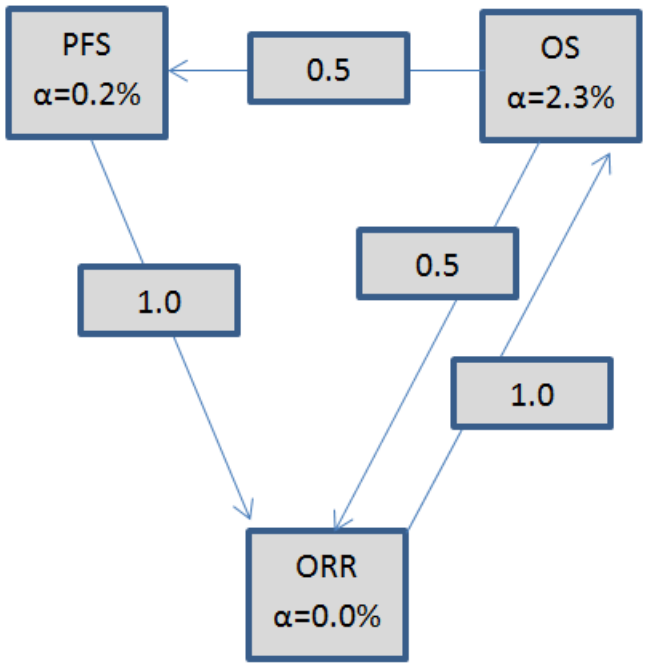
Results of the interim analyses will be reviewed by the eDMC. If the OS null hypothesis is rejected prior to the final analysis, the eDMC may recommend stopping the study early for efficacy. Details on how the above planned analyses are incorporated into establishing Type I error control and efficacy boundaries are discussed further in Section 9.8 – Multiplicity.

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests.

Figure 3 shows the initial one-sided α allocation for each hypothesis in the box representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

Figure 3 Multiplicity Graph for Type I Error Control



ORR = objective response rate; OS = overall survival; PFS = progression-free survival

9.8.1 Progression-free Survival

The initial α-level for testing PFS is 0.002. If the null hypothesis for OS is rejected, Figure 3 shows that 0.5 of OS initial α=0.023 (ie, α=0.0115) is reallocated to PFS hypothesis testing. If the null hypothesis for OS and the null hypothesis for ORR are both rejected, then α=0.023 is reallocated to PFS hypothesis testing. Thus, the PFS null hypothesis may be tested at α=0.002, α=0.0135 (if only the OS null hypothesis is rejected), or α=0.025 (if both the ORR and OS null hypotheses are rejected). Table 16 shows the boundary properties for 3 possible 1-sided α-levels for the final analysis, which were derived using a Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for PFS. If the actual number of events at the PFS analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly. Also, note that if the OS null hypothesis is rejected at an interim or final analysis, PFS interim and final analysis tests will be compared to the updated PFS bounds considering the α reallocation from the OS hypothesis.

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

Analysis	Value	α level=0.002	α level=0.0135	α level=0.025
IA1: 83%[a]	Z	3.1972	2.4731	2.2006
N: 750	p (1-sided)[b]	0.0007	0.0067	0.0139
Events: 474	HR at bound[c]	0.7454	0.7965	0.8169
Month: 27.5	P(Cross) if HR=1[d]	0.0007	0.0067	0.0139
	P(Cross) if HR=0.7[e]	0.7559	0.9207	0.9538
IA2	Z	2.9135	2.2721	2.0334
N: 750	p (1-sided)	0.0018	0.0115	0.0210
Events: 571	HR at bound	0.7835	0.8266	0.8434
Month: 35.6	P(Cross) if HR=1	0.0020	0.0135	0.0250
	P(Cross) if HR=0.7	0.9150	0.9782	0.9882

HR = hazard ratio; IA1 = Interim Analysis 1.
[a] Expected percentage of events with respect to the number of events expected at the final analysis.
[b] p (1-sided) is the nominal α for testing.
[c] HR at bound is the approximate HR required to reach an efficacy bound.
[d] P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[e] P (Cross if HR=0.7) is the probability of crossing a bound under the alternative hypothesis.

9.8.2 Overall Survival

The OS hypothesis may be tested at α=0.023 (initially allocated α) or α=0.025 (if both the ORR and PFS null hypotheses are rejected). Table 17 demonstrates the bounds and properties for OS hypothesis testing derived using a Lan-DeMets O'Brien-Fleming spending function with the initial α-level of 0.023 or α=0.025 (if both the ORR and PFS null hypotheses are rejected) for the final analysis. If the actual number of OS events at the interim and final

analyses differs from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly.

Table 17 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	**Value**	**α level=0.023**	**α level=0.025**
IA1: 63%[a]	Z	2.6372	2.5939
N: 750	p (1-sided) [b]	0.0042	0.0047
Events: 335	HR at bound[c]	0.7495	0.7531
Month: 27.4	P(Cross) if HR=1[d]	0.0042	0.0047
	P(Cross) if HR=0.75[e]	0.4987	0.5161
IA2: 85%	Z	2.2448	2.2085
N: 750	p (1-sided)	0.0124	0.0136
Events: 452	HR at bound	0.8095	0.8124
Month: 35.6	P(Cross) if HR=1	0.0137	0.0151
	P(Cross) if HR=0.75	0.7975	0.8080
Final	Z	2.0808	2.0478
N: 750	p (1-sided)	0.0187	0.0203
Events: 532	HR at bound	0.8348	0.8372
Month: 43.6	P(Cross) if HR=1	0.0230	0.0250
	P(Cross) if HR=0.75	0.9000	0.9060

HR = hazard ratio; IA1 = Interim Analysis 1; IA2 = Interim Analysis 2.
[a] Expected percentage of events with respect to the number of events expected at the final analysis.
[b] p (1-sided) is the nominal α for testing.
[c] HR at bound is the approximate HR required to reach an efficacy bound.
[d] P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[e] P (Cross if HR=0.7) is the probability of crossing a bound under the alternative hypothesis.

9.8.3 Objective Response

The OR hypothesis is not allocated any α initially and can only be tested when either the PFS or OS endpoint is successful. The OR data obtained at the time of IA1 will be locked and tested at the time when α to test the OR hypothesis becomes available; it will be retested if available α increases. Specifically, if the OR test does not achieve statistical significance at IA1, the p-value from IA1 can be compared to an updated α-level at a later time. The power and smallest statistically significant detectable difference at the 3 possible α-levels, assuming underlying 19% and 30% response rates in the lenvatinib and pembrolizumab plus lenvatinib groups, respectively, are shown in Table 18 with 750 randomized participants.

Table 18 Possible Alpha-levels and Power for ORR Analysis

Value	**α level= 0.002**	**α level=0.0115**	**α level=0.025**
Smallest Statistically Significant Detectable Difference in ORR	0.0903	0.0712	0.0614
Power if Difference in ORR=0.11	0.74	0.89	0.94
ORR = objective response rate.			

9.8.4 Safety Analyses

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

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

The study will randomize 750 participants in a 1:1 ratio into the pembrolizumab plus lenvatinib or placebo plus lenvatinib arms. For the OS endpoint, based on a target number of 532 events and 2 interim analyses at approximately 63% and 85% of the target number of events, the study has approximately 90% power to detect an HR of 0.75 at an overall alpha level of 2.3% (1-sided). For the PFS endpoint, based on the expected number of 571 events at the final analysis and 1 interim analysis at approximately 83% of the target number of events, the study has approximately 92% power to detect an HR of 0.70 at an overall alpha level of 0.2% (1-sided).

The sample size and power calculations for PFS and OS assume the following:

- PFS follows an exponential distribution with a median of 7.3 months for the control group.
- OS follows an exponential distribution in both arms with a median of 14.5 months for the control group. The HR of 0.75 would result in 19.3 months for median OS for the combination group. Constant HR for PFS and OS endpoints.
- Enrollment period of 21 months with a ramp-up period of 9 months.
- A monthly drop-out rate of 0.01 and 0.001 for PFS and OS, respectively.

With these assumptions, the final OS analysis will take place 44 months after the start of randomization.

Based on the 750 participants, the power of the ORR testing at the reallocated from PFS α=0.002 is approximately 74% to detect a difference between an underlying 19% ORR in the control arm and a 30% ORR in the experimental arm.

9.9.2 Sample Size and Power for Safety Analyses

For safety comparisons, risk differences between any 2 treatment groups are summarized in Table 19 for a variety of hypothetical observed incidence rates. The table demonstrates the width of the corresponding 95% CIs for different incidence rates in the treatment groups. These calculations assume there are 375 participants for each treatment group.

Table 19 Two-sided 95% CIs of Differences in Incidence of AE Rates Between the Two Treatment Groups for 375 Participants in Each Treatment Arm

Incidence of Adverse Event		**Risk Difference**	
Treatment Group 1 (%)	Treatment Group 2 (%)	Percentage Points	95% Confidence Interval[a]
5.1	12.3	-7.2	(-11.2, -3.2)
11	20.2	-9.2	(-14.4, -4.0)
24.9	36.6	-11.7	(-18.3, -5.1)
43.9	56.5	-12.6	(-19.7, -5.5)
55.7	68	-12.3	(-19.2, -5.4)

Incidences presented here are hypothetical and do not represent actual adverse experiences in either group.
[a] Based on an asymptotic method [Farrington, C. P. 1990].

9.10 Subgroup Analyses

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

- Stratification factors
  - Geographic region (Region 1: Asia vs. Region 2: Japan and Western regions, such as EU, North America, etc.)
  - Macroscopic portal vein invasion or extrahepatic spread or both (Yes vs. No)
  - AFP: ≤400 ng/mL versus >400 ng/mL
  - ECOG PS: 0 vs. 1

- Age category (<65, ≥65 years)
- Sex (female, male)
- Etiology (HCV, HBV, and uninfected)
- Macrovascular invasion (Yes, No)
- Extrahepatic spread (Yes, No)
- Current disease overall BCLC stage (B, C)
- CP score (5 vs 6)

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including signed ICF, 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. 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 may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 20 will be performed by the local laboratory with the exception of hepatitis testing, which will be performed by the central laboratory.
- 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.

Table 20 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	Magnesium	Phosphorous
	Amylase	Lipase[e]	Lactate Dehydrogenase	Triglycerides
	GGT			
Urinalysis/Urine dipstick testing	• Specific gravity • pH, glucose, protein, blood (or hemoglobin), ketones, by dipstick[f]			

Laboratory Assessments	Parameters
Other Tests	• Serology Anti-HCV (IgG), HCV viral load, HCV genotype, anti-HBs, HBsAg, Anti-HBc (total and IgM), Anti-HBe, HBeAg, HBV viral load, HDV RNA, and Anti-HDV[g] • PT/INR • AFP • Serum or urine Pregnancy test • Thyroid-stimulating Hormone (TSH)[h], Free thyroxine (FT4)[h], Triiodothyronine (T3)[h] • Serology HIV antibody as required by local health authority or institutional regulations. Refer to Appendix 7 for country-specific information.

Abbreviations: AFP = alpha fetaprotein; Anti-HBc = antihepatitis B core antibody, Total; Anti-HBs = antihepatitis B surface antibody; Anti-HDV = antihepatitis D antibody; GGT = gamma-glutamyl transferase; HBeAg = hepatitis B early antigen; 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; 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] After Cycle 1, retrospective review of lipase results is allowed when the results are not available prior to dosing.

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

[g] 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), Anti-HBe, HBeAg, HBV viral load, HDV RNA and Anti-HDV), which will be done centrally.

[h] Free T4, T3, and TSH levels will be performed as indicated in Section 1.3 (SoA). T3: T3 is preferred; if not available, Free T3 may be tested. There may be instances when sites are unable to obtain the thyroid function testing results 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 patient.

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study).

  Note: Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events

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

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- 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 Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. 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 activities of daily living (ADL).

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare 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 AE, SAE, and Other Reportable Safety Events to the Sponsor

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

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

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

10.5.2 Contraception Requirements

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

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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Germany

Section 1.3 Schedule of Activities

Study Period	**Screening[a]**	**Treatment Period 42-Day Cycles**										**EOT**	**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**		
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		
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

30. Participant has a known history of human immunodeficiency virus (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 42-Day Cycles**										**EOT**	**Notes**
Intervention Cycles/ Titles		**1**			**2**		**3**	**4**	**5**	**6**	**7 to last**		
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**		
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

30. Participant has a known history of human immunodeficiency virus (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 France

Section 6.6.2 Pembrolizumab Dose Modification

Stevens-Johnson Syndrome is a permanent discontinuation criterion for pembrolizumab for France.

10.7.4 China

Biomarker sample collection, testing, and analysis as described in the following sections will be dependent on approval by the Human Genetic Resources Administration of China for participants enrolled in China:

- Section 1.3: Schedule of Activities
- Section 4.2.1.6: Planned Exploratory Biomarker Research
- Section 5: Inclusion Criteria, Exclusion Criteria
- Section 8.8: Biomarkers

Future biomedical research will not be conducted in China.

10.7.5 Japan

Section 6.1 Study Intervention(s) Administered

Lenvatinib used in this study is categorized as “product(s) used in the clinical trial 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 trial” in Japan.

10.8 Appendix 8: Hepatitis B Definitions and Treatment Considerations

Table 21 describes the various definitions of treatment considerations and eligibility for study participation, along with the definitions of hepatitis B.

Table 21 Hepatitis B Definitions and Treatment Considerations

Test	Patient Status	Eligible for MK-7902-002?	Any HBV Treatment Needed?
HBsAg (–) Total anti-HBc (+) HBsAb (+)	Immune after natural infection	Yes	No
HBsAg (–) Total anti-HBc (–) HBsAb (+)	Immune after vaccination	Yes	No
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (+) HBsAb (–)	Acute infection	No	—
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–)	Chronic infection	Yes	Yes, need to be on a HBV treatment for at least 4 weeks prior to start of study treatment without evidence of a flare during that period Exclude if: (a) <4 weeks of therapy; (b) HBV viral load not under control during this time frame; (c) Documented HBV flare in the past 4 weeks
HBsAg (–) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–) HBV viral load (negative)	Unclear. Could be: • Resolved infection • False positive anti-HBc • Low level infection • Resolving acute infection	Yes	No
HBsAg (–) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–) HBV viral load (+)	• Low level infection • Resolving acute infection	Yes	Yes (as above)

Anti-HBc = antihepatitis B core antibody, HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgM = immunoglobulin M.

10.9 Appendix 9: ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, PPD , Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out 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
*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 Prothrombin time, prolongation (seconds)	<1.7 <4.0 above ULN	1.7 to 2.3 4.0-6.0 above ULN	> 2.3 >6.0 above ULN
Ascites	None	Mild (easily controlled by medication)	Moderate to Severe (poorly controlled)
Hepatic encephalopathy[d]	None	Grade I-II (mild or moderate)	Grade III-IV (severe or coma)

[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 patients on anticoagulants (eg, Coumadin), only 1 point is assigned irrespective of the patient'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 semi-stupor, but responsive to verbal stimuli

  Confusion; Gross disorientation
- Grade IV: Coma (unresponsive to verbal or noxious stimuli)

Interpretation

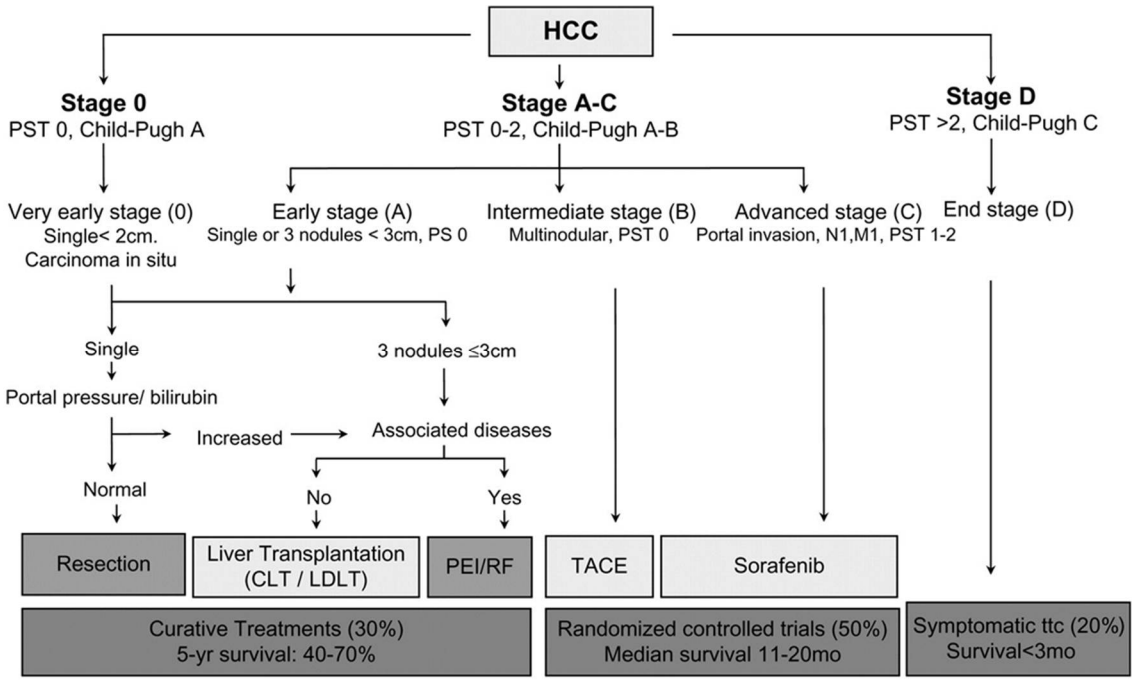
Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

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 4 below [Llovet, J. M., et al 2008].

Figure 4 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 New York Heart Association (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: Clinical Studies Evaluating Drug-Drug Interactions With Lenvatinib

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

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

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

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

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

10.14 Appendix 14: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management (see Table 8 and Figure 2). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit or if RECIST 1.1 PD has not been verified centrally, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudo-progression Resolves

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

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

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

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

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

10.15 Appendix 15: American Association for the Study of Liver Diseases (AASLD) Liver Imaging Reporting and Data System (LI-RADS) 5 Criteria

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

Table 22 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].

10.16 Appendix 16: Abbreviations

Abbreviation	Expanded Term
1L	First-line
2L	Second-line
AASLD	American Association for the Study of Liver Diseases
ADA	Anti-drug antibodies
ADL	Activities of daily living
AE	Adverse event
AEOSI	Adverse event of special interest
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core antibody, Total
Anti-HBc, IgM	Hepatitis B core antibody, IgM
Anti-HBe	Hepatitis B early 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 concentration-time curve
BCG	Bacillus Calmette–Guérin
BCLC	Barcelona Clinic Liver Cancer
BICR	Blinded independent central [imaging] review(ers)
BP	Blood pressure
BW	Body weight
C1D1	Cycle 1 Day 1
CD	Cluster of differentiation
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form
CP	Child-Pugh
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CYP	Cytochrome P450
D/C	Discontinuation/Discontinuing
DC	Disease Control
DCR	Disease control rate
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	European Commission
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
ECI	Event of clinical interest
eCRF	Electronic Case Report Form
EDC	Electronic data collection
EMA	European Medicines Agency

Abbreviation	Expanded Term
EOC	Executive Oversight Committee
EORTC	European Organisation for the Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life 5-dimension, 5-level Questionnaire
EU	European Union
EuroQOL	European Quality of Life
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FOLFOX	chemotherapy regimen containing: folinic acid, 5 fluorouracil, and oxaliplatin
GCP	Good Clinical Practice
HBeAg	Hepatitis B early antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HECI	Hepatic event of clinical interest
HGRAC	Human Genetics Resources Administration of China
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HRT	Hormone replacement therapy
HDV	Hepatitis D virus
IA1	Interim Analysis 1
IA2	Interim Analysis 2
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iCPD	iRECIST confirmed radiographic progression
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalized ratio
IPCW	Inverse probability of censoring weight
iPD	iRECIST confirmed progressive disease
IRB	Institutional Review Board
irAE	Immune-related adverse events
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	Interactive response technology
ITT	Intention-to-treat
iUPD	iRECIST unconfirmed progressive disease
IV	Intravenous(ly)
LVEF	Left ventricular ejection fraction
mAB	Monoclonal antibody
mRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Nonsmall cell lung cancer

Abbreviation	Expanded Term
NYHA	New York Heart Association
ONJ	Osteonecrosis of the jaw
OR	Objective Response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
P-gp	p-Glycoprotein
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
PS	Performance Status
PRES/RPLS	Posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome
Q12W	Every 12 weeks
Q3W	Every 3 weeks
Q9W	Every 9 weeks
QD	Once daily
QLQ	Quality of life Questionnaire
QOD	Every other day
QoL	Quality of life
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RTK	Receptor tyrosine kinase
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
sSAP	Supplemental SAP
TEA	Treatment eligibility assessment
TEAE	Treatment-emergent AEs
TTD	Time to deterioration
TTP	Time to progression
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
Vp4	Main portal of portal vein
WOCBP	Woman/women of childbearing potential

11 REFERENCES

[Aaronson, N. K., et al 1993]	Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.	[03Q3QL]
[Abd El-Kader, S. M. 2015]	Abd El-Kader SM, El-Den Ashmawy EM. Non-alcoholic fatty liver disease: The diagnosis and management. World J Hepatol. 2015 Apr 28;7(6):846-58.	[04R886]
[Abou-Alfa, G. K., et al 2018]	Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: results from the randomized phase III CELESTIAL trial [abstract]. J Clin Oncol. 2018 Feb;36(4 suppl):207.	[04WMBS]
[Blazeby, J. M., et al 2004]	Blazeby JM, Currie E, Zee BC, Chie WC, Poon RT, Garden OJ, et al. Development of a questionnaire module to supplement the EORTC QLQ-C30 to assess quality of life in patients with hepatocellular carcinoma, the EORTC QLQ-HCC18. Eur J Cancer. 2004 Nov;40(16):2439-44.	[0497ZV]
[Bruix, J., et al 2017]	Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 7;389(10064):56-66.	[04LSRJ]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]

[Cheng, A.-L., et al 2009]	Cheng A-L, Kang Y-K, Chen Z, Tsao C-J, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.	[03RHVT]
[Cross, M. J. and Claesson-Welsh L. 2001]	Cross MJ, Claesson-Welsh L. FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition. Trends Pharmacol Sci. 2001 Apr;22(4):201-7.	[04XKP6]
[Dhanasekaran, R., et al 2012]	Dhanasekaran R, Limaye A, Cabrera R. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis, and therapeutics. Hepat Med. 2012 May 8;4:19-37.	[04R8N7]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dolgin, M., et al 1994]	Dolgin M, Fox AC, Gorlin R, Levin RI, editors. Functional capacity and objective assessment. In: Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little, Brown; 1994. p. 253–5.	[04TSK5]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[El-Khoueiry, A. B., et al 2017]	El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017 Jun 24;389(10088):2492-2502.	[04QPD8]
[Ellis, L. M. and Hicklin, D. J. 2008]	Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008 Aug;8:579-91.	[04XKPD]

[Farrington, C. P. 1990]	Farrington CP, Manning G. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk. Stat Med Vol. 9,1447-1454 (1990)	[04FS6L]
[Ferlay, J., et al 2015]	Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86.	[043HC4]
[Ferrara, N., et al 2003]	Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003 Jun;9(6):669-76.	[04XKQ2]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Gao, Q., et al 2009]	Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res. 2009 Feb 1;15(3):971-9.	[046X5W]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Hoshida, Y., et al 2008]	Hoshida Y, Villanueva A, Kobayashi M, Peix J, Chiang DY, Camargo A, et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. N Engl J Med. 2008 Nov 6;359(19):1995-2004.	[049567]

[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Iavarone, M., et al 2011]	Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology. 2011 Dec;54(6):2055-63.	[048QMY]
[Ikeda, M., et al 2018]	Ikeda M, Sung MW, Kudo M, Kobayashi M, Baron AD, Finn RS, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC). Poster session presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. Poster no. 4076.	[04YJ9K]
[Katagiri. S. 2014]	Katagiri S, Yamamoto M. Multidisciplinary treatments for hepatocellular carcinoma with major portal vein tumor thrombus. Surg Today. 2014;44:219-26.	[050SKG]
[Kato, Y., et al 2015]	Kato Y, Tabata K, Hori Y, Tachino S, Okamoto K, Matsui J, et al. Effects of lenvatinib on tumor-associated macrophages enhance antitumor activity of PD-1 signal inhibitors [abstract A92]. Poster session presented at: AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2015 Nov 5-6; Boston, MA.	[04T3PH]
[Kato, Y., et al 2016]	Kato Y, Bao X, Macgrath S, Tabata K, Hori Y, Tachino S, et al. Lenvatinib mesilate (LEN) enhanced antitumor activity of a PD-1 blockade agent by potentiating Th1 immune response [abstract]. Ann Oncol. 2016;27(6 Suppl). Abstract no. 2PD.	[04QHX2]

[Kudo, M., et al 2018]	Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. In press 2018.	[04W029]
[Kuo, Y. H., et al 2018]	Kuo YH, Wu IP, Wang JH, Hung CH, Rau KM, Chen CH, et al. The outcome of sorafenib monotherapy on hepatocellular carcinoma with portal vein tumor thrombosis. Invest New Drugs. 2018;36:307-14.	[050SKJ]
[Lafaro, K. J., et al 2015]	Lafaro KJ, Demirjian AN, Pawlik TM. Epidemiology of hepatocellular carcinoma. Surg Oncol Clin N Am. 2015 Jan;24(1):1-17.	[0483RD]
[Lencioni, R. 2010]	Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010 Feb;30(1):52-60.	[04960X]
[Lencioni, R. 2010]	Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010 Feb;30(1):52-60.	[04SSDP]
[Lieu, C., et al 2011]	Lieu C, Heymach J, Overman M, Tran H, Kopetz S. Beyond VEGF: inhibition of the fibroblast growth factor pathway and antiangiogenesis. Clin Cancer Res. 2011 Oct 1;17(19):6130-9.	[04XKQM]
[Limaverde-Sousa, G., et al 2014]	Limaverde-Sousa G, Sternberg C, Ferreira CG. Antiangiogenesis beyond VEGF inhibition: a journey from antiangiogenic single-target to broad-spectrum agents. Cancer Treat Rev. 2014;40:548-57.	[04XKQW]
[Llovet, J. M., et al 2008]	Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008 May 21;100(10):698-711.	[048QRV]

[Llovet, J. M., et al 2013]	Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol. 2013 Oct 1;31(28):3509-16.	[048NHG]
[Llovet, Josep M., et al 2008]	Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378-90.	[03R8N8]
[Makarova-Rusher, O. V., et al 2016]	Makarova-Rusher OV, Altekruse SF, McNeel TS, Ulahannan S, Duffy AG, Graubard BI, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. Cancer. 2016 Jun 1;122(11):1757-65.	[04R8B9]
[Makker, V., et al 2021]	Makker V, Taylor MH, Oaknin A, Casado Herraez A, Orlowski R, Dutta L, et al. Characterization and management of adverse reactions in patients with advanced endometrial carcinoma treated with lenvatinib plus pembrolizumab. Oncologist. 2021;26:e1599-608.	[07WK86]
[Marrero, J. A., et al 2018]	Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Aug;68(2):723-50.	[056Z3B]
[Matsuki, M., et al 2018]	Matsuki M, Hoshi T, Yamamoto Y, Ikemori-Kawada M, Minoshima Y, Funahashi Y, et al. Lenvatinib inhibits angiogenesis and tumor fibroblast growth factor signaling pathways in human hepatocellular carcinoma models. Cancer Med. In press 2018.	[04YJ9R]
[Maurer, W. and Bretz, F. 2013]	Maurer W and Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.	[03XQVB]

[McGlynn, K. A., et al 2015]	McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis. 2015 May;19(2):223-38.	[047WD5]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Petrick, J. L., et al 2016]	Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. J Clin Oncol. 2016 May 20;34(15):1787-94.	[04R37B]
[Pickard, A. S., et al 2007]	Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:1-8.	[00W0FM]
[Poon, R. T. P., et al 2004]	Poon RTP, Ho JWY, Tong CSW, Lau C, Ng IOL, Fan ST. Prognostic significance of serum vascular endothelial growth factor and endostatin in patients with hepatocellular carcinoma. Br J Surg. 2004;91:1354-60.	[04YJ9T]
[Qin, S., et al 2013]	Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol. 2013 Oct 1;31(28):3501-8.	[048ND5]

[Rabin, R. and de Charro, F. 2001]	Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43.	[03QM46]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Sangro, B., et al 2013]	Sangro B, Gomez-Martin C, de la Mata M, Inarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol. 2013 Jul;59(1):81-8.	[048QS9]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Shi, F., et al 2011]	Shi F, Shi M, Zeng Z, Qi RZ, Liu ZW, Zhang JY, et al. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. Int J Cancer. 2011 Feb 15;128(4):887-96.	[046XYK]
[Shumaker, R. C., et al 2014]	Shumaker RC, Aluri J, Fan J, Martinez G, Thompson GA, Ren M. Effect of rifampicin on the pharmacokinetics of lenvatinib in healthy adults. Clin Drug Investig. 2014 Sep;34(9):651-9.	[04SJ7D]
[Shumaker, R., et al 2015]	Shumaker R, Aluri J, Fan J, Martinez G, Thompson GA, Ren M. Effects of ketoconazole on the pharmacokinetics of lenvatinib (E7080) in healthy participants. Clin Pharmacol Drug Dev. 2015 Mar;4(2):155-60.	[04SJ85]

[Tammela, T. and Alitalo, K. 2010]	Tammela T, Alitalo K. Lymphangiogenesis: molecular mechanisms and future promise. Cell. 2010 Feb 19;140:460-76.	[04XKRB]
[Welzel, T. M., et al 2013]	Welzel TM, Graubard BI, Quraishi S, Zeuzem S, Davila JA, El-Serag HB, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol. 2013 Aug;108(8):1314-21.	[04907K]
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[Yamaguchi, R., et al 1998]	Yamaguchi R, Yano H, Iemura A, Ogasawara S, Haramaki M, Kojiro M. Expression of vascular endothelial growth factor in human hepatocellular carcinoma. Hepatology. 1998 Jul;28(1):68-77.	[04YJB9]
[Yamamoto, Y., et al 2014]	Yamamoto Y, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014;6:18.	[04YJBQ]
[Yang, J. C., et al 2013]	Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TSK, et al. Symptom control and quality of life in LUX-Lung 3: A phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31(27):3342-50.	[03NDT4]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]

[Zhu, A. X., et al 2018]	Zhu AX, Finn RS, Cattan S, Edeline J, Ogasawara S, Palmer DH, et al. KEYNOTE-224: pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib [abstract]. Poster session presented at: 2018 Gastrointestinal Cancers Symposium; 2018 Jan 18-20; San Francisco, CA. J Clin Oncol. 2018;36(suppl 4):209.	[04W24S]
[Zhu, A. X., et al 2018]	Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. In press 2018.	[04YDRF]
[Zhu, A. X., et al 2018]	Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. REACH-2: a randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib [abstract]. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018 May 20;36(15 suppl). Abstract no. 4003.	[04YXT7]