Official Protocol Title:	A Phase 3 Double-blinded, Two-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) versus Placebo as Adjuvant Therapy in Participants with Hepatocellular Carcinoma and Complete Radiological Response after Surgical Resection or Local Ablation (KEYNOTE-937)
NCT number:	NCT03867084
Document Date:	08-Dec-2022

Title Page

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Protocol Title: A Phase 3 Double-blinded, Two-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) versus Placebo as Adjuvant Therapy in Participants with Hepatocellular Carcinoma and Complete Radiological Response after Surgical Resection or Local Ablation (KEYNOTE-937)

Protocol Number: 937-08

Compound Number: MK-3475

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	123,482
EudraCT	2018-004800-20
EU CT	2022-501971-24-00

Approval Date: 08 December 2022

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 08	08-DEC-2022	To update the statistical analysis strategy [redacted]
Amendment 07	22-JUN-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 6	22-FEB-2022	To update the statistical analysis strategy, change the multiplicity strategy to a step-down alpha allocation approach from RFS to OS to increase the power for RFS, [redacted]
Amendment 5	07-JUN-2021	To update the dose modification and toxicity management guidelines for irAEs and incorporate previously approved site-specific amendment at selected sites in the United States of America (USA) for translational oncology research (TOR) and country-specific amendment for Korea, as appendices.
Amendment 4	24-NOV-2020	[redacted]
Amendment 3	17-DEC-2020	Site-specific amendment at selected sites in the USA to include requirement for [redacted] at these selected sites is not mandatory for all participants.

Document	Date of Issue	Overall Rationale
Amendment 2	31-JUL-2020	Updated enrollment and inclusion criteria and addressed feedback from sites.
Amendment 1	02-AUG-2019	Updated statistical analysis plan [redacted], updated timing and number of interim analyses, [redacted], and clarified sections of the protocol based on feedback from sites.
Original Protocol	18-JAN-2019	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendments:

To update the statistical analysis strategy accounting for CCI [redacted]

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
4.1 – Overall Design 4.2 – Scientific Rationale for Study Design 4.2.1.1 – Efficacy Endpoints 9.1 – Statistical Analysis Plan Summary 9.7.2 – Efficacy Interim Analyses 9.8 – Multiplicity 9.8.1 – Recurrence-free Survival 9.8.2 – Overall Survival 9.9.1 – Sample Size and Power for Efficacy Analyses	The timing and number of events at interim and final analyses are updated. CCI [redacted]	Analyses plan updated CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
Title Page	Added EU CT Number	Revision to align with the EU clinical trial regulation (CTR) No. 536/2014 of the European Parliament and of the Council
4.4 – Beginning and End of Study Definition	Added clarifying text	
6.1 – Study Intervention(s) Administered	Table 3 Study Interventions Use updated from Experimental to Test Product and IMP/NIMP updated to IMP or NIMP/AxMP	
10.3.1 – Definition of Medication Error, Misuse, and Abuse	Definition of Medication Error, Misuse, and Abuse added	
1.3 – Schedule of Activities (SoA) 10.5.3 – Pregnancy Testing	Added clarifying text regarding pregnancy testing if new anticancer treatment is started	To clarify when pregnancy testing should be performed
8.2.1 – Tumor Imaging and Assessment of Disease 8.2.1.3 – End-of-Treatment and Follow-up Tumor Imaging	Added clarifying text	To clarify imaging requirements and provide an option for submitting standard of care scans during follow-up or continue in the Efficacy Follow-up Phase
8.2.2 – Patient-reported Outcomes	Updated timing of PRO collection	To clarify timing
9.4.3 – PRO Endpoints 9.5.3 – PRO Analysis Populations 9.6.3 – Statistical Methods for Patient-reported Outcome Analyses	Added a brief description of the PRO analyses	To provide the description of analyses of these secondary endpoints

Section # and Name	Description of Change	Brief Rationale
9.6.1 – Statistical Methods for Efficacy Analyses	Added clarifying text	To clarify the methodology
9.6.2 – Statistical Methods for Safety Analyses	Updated safety analyses methods	Methodology across the studies pembrolizumab program has been streamlined by the Sponsor
9.10 – Subgroup Analyses	Added clarifying text	To clarify the derivation of subgroups
10.2 – Appendix 2: Clinical Laboratory Tests	Specific test parameters moved to "Other test" in Table 14 Added clarifying text to footnote 'e'	To clarify the type of testing
10.5.2 – Contraception Requirements	Removed Footnote c	To correct an error in the previous amendment
10.7.1 – China	Removed Recurrent Grade 3 colitis	To correct an error in the previous amendment
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document	To ensure clarity and accurate interpretation of the intent of the protocol

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Double-blinded, Two-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) versus Placebo as Adjuvant Therapy in Participants with Hepatocellular Carcinoma and Complete Radiological Response after Surgical Resection or Local Ablation (KEYNOTE-937)

Short Title: Adjuvant Therapy with Pembrolizumab Versus Placebo in Participants with Hepatocellular Carcinoma and Complete Radiological Response after Surgical Resection or Local Ablation

Acronym: KEYNOTE-937

Hypotheses, Objectives, and Endpoints:

In participants at least 18 years of age with hepatocellular carcinoma (HCC) and complete radiological response after surgical resection or local ablation:

Primary Objectives	Primary Endpoints
Objective: To compare recurrence-free Survival (RFS). Hypothesis (H1): Pembrolizumab is superior to placebo with respect to RFS as assessed by blinded independent central review (BICR).	RFS: the time from randomization to first documentation of disease recurrence (local, regional, or distant) as assessed by BICR or by pathology consistent with HCC, or death due to any cause (both cancer and non-cancer causes of death), whichever occurs first.
Objective: To compare overall survival (OS). Hypothesis (H2): Pembrolizumab is superior to placebo with respect to OS.	OS: The time from randomization to death due to any cause.
Secondary Objectives	Secondary Endpoints
Objective: To evaluate the safety and tolerability.	Adverse events (AEs). Study intervention discontinuation due to AEs.
Objective: To compare score change from baseline in global quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health status/QoL scale and EORTC QLQ-HCC18.	Scores from the global health status/ quality of life (QoL) scale on the EORTC QLQ-C30 and EORTC QLQ-HCC18.

Objective: To characterize health utilities using the EuroQoL-5 Dimension Questionnaire, 5-Level (EQ-5D-5L) healthy utility scores.	EQ-5D-5L health utility score.

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Adjuvant treatment of HCC
Population	Participants with complete radiological response after surgical resection of Stage IB, II, and III HCC per American Joint Committee on Cancer (AJCC) 8th Edition with adaptations based on tumor characteristics as established by the pathology report or complete radiological response after local ablation
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Masking	Investigator Participant
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 10 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact

Number of Participants:

Approximately 950 participants will be randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Fre-quency</th><th>Route of Admini-stration</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td>Pembrolizumab</td><td>Pembrolizumab (MK-3475)</td><td>200 mg on Day 1 of each cycle</td><td>Q3W</td><td>IV</td><td>17 administrations (approximately 1 year)</td><td>Experimental</td></tr>
<tr><td>Placebo</td><td>Saline solution</td><td>on Day 1 of each cycle</td><td>Q3W</td><td>IV</td><td>17 administrations (approximately 1 year)</td><td>Placebo Comparator</td></tr>
<tr><td colspan="7">IV=intravenous; Q3W=every 3 weeks</td></tr>
</table>
Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-3475, Keytruda®
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2 interventions</td></tr>
</table>

Duration of Participation	Each participant will participate in the study for approximately 6 years from the time the participant provides documented informed consent through the final contact. After a screening phase of 28 days, each participant will be receiving assigned intervention to 17 administrations (approximately 1 year). After the end of treatment, each participant will be followed for 30 days for AEs. Serious adverse events will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier. Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. After a screening phase, each participant will be assigned to receive study intervention (pembrolizumab or placebo) until disease recurrence is documented by investigator and verified by BICR, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, administrative reasons requiring cessation of treatment, or until the participant has received 17 administrations of pembrolizumab or placebo (approximately 1 year). Disease recurrence will be documented by investigator radiographically (with site radiologist) and will be verified by BICR. Disease recurrence will be verified by BICR prior to DC of study intervention. No cross-over is allowed in this study. For participants who DC for reasons other than BICR-verified disease recurrence or BICR-verified intra-hepatic recurrence, imaging should continue to be performed as if on study until extra-hepatic disease recurrence has been verified by BICR. Disease recurrence can also be confirmed with pathology if required per the site's standard of care. After the end of study treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4.4. Participants who initiate a new non-study cancer treatment should continue to have post-treatment distant metastases-free survival (DMFS) follow-up until extra-hepatic disease recurrence is documented by investigator (radiographically and/or with subsequent pathology) and verified by BICR. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

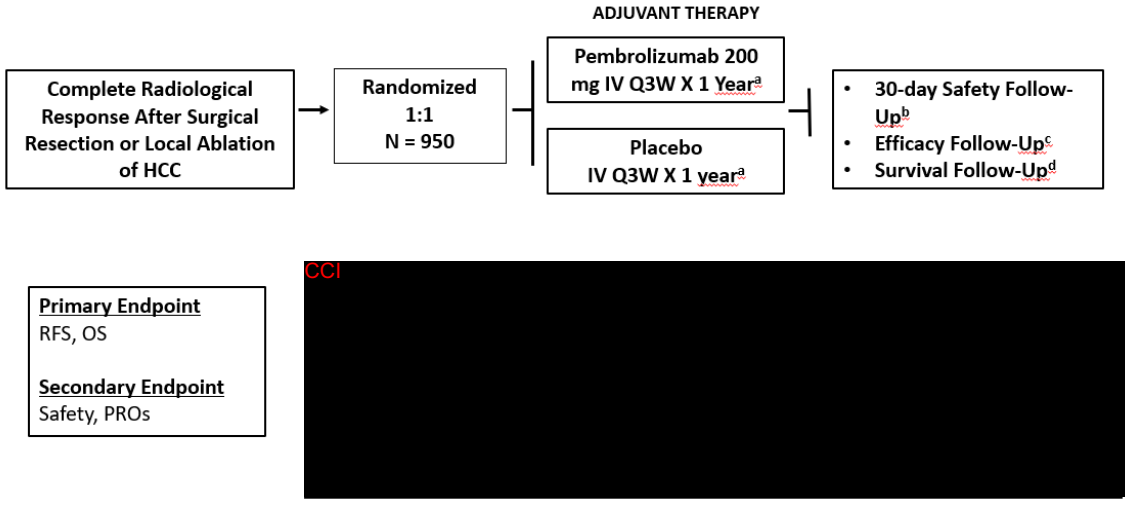
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 15.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram



AFP=alpha fetoprotein; HCC=hepatocellular carcinoma; IV=intravenous; OS=overall survival; PROs=patient-reported outcomes; Q3W=every 3 weeks; Q12W=every 12 weeks; RFS=recurrence-free survival.

a. Randomization needs to occur within 12 weeks of surgical resection or local ablation. Imaging during study intervention to be performed Q12W after randomization (±7 days) until Week 52 (~Year 1).

b. If End-of-Treatment visit occurs ≥30 days after last dose of study intervention, a Safety Follow-up Visit is not required.

c. Imaging should be performed per Section 8.2.1.2.

d. Participants in Survival Follow-up will be contacted approximately Q12W or sooner to assess for survival status or death, withdrawal of consent, or the end of study, whichever occurs first.

1.3 Schedule of Activities (SoA)

Table 1 Study Schedule of Activities

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Administrative Procedures												
Informed Consent	X											Consent form can be obtained at any time prior to any protocol-specific screening procedures being performed.
Informed Consent/ for Future Biomedical Research	X											This is optional for the participant.
Inclusion/ Exclusion Criteria	X											

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Participant Identification Card	X	X										Add the randomization number at the time of allocation or randomization. Place a tick mark in the visit where consent occurs, and also where randomization occurs (or one if both occur at the same visit).
Medical/Surgical History (including HCV therapy, smoking, and alcohol use) and Demographics	X											Significant medical/surgical history, including HCV therapy, will be captured for last 10 years.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
AJCC Staging	X											Staging at the time of initial diagnosis prior to resection or local ablation as well as post resection staging based on AJCC 8th edition. See Appendix 10.
BCLC Staging	X											Staging at the time of initial diagnosis prior to resection or local ablation. See Appendix 11.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Prior and Concomitant Medication Review	X	X	X	X	X	X						Record all prior medications taken within 28 days before C1D1. Enter new medications started during the study through the Safety Follow-up. Record concomitant medications beyond 30 days after treatment discontinuation if related to SAE or ECI.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Study Intervention												
Randomization and study intervention assignment via IRT		X										Randomization must be completed after confirmation of eligibility. C1D1 must occur within 3 days of randomization. Exceptionally, randomization can occur within 5 days of C1D1 upon discussion with the Sponsor.
Pembrolizumab (MK-3475) / Placebo Administration		X	X	X								Pembrolizumab 200 mg Q3W or Placebo Q3W for up to 17 cycles.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Anticancer Therapy Status						X	X	X	X	X	X	Any changes in new treatment will be collected. If a clinic visit is not feasible, follow-up information may be obtained via other means of contact (eg. telephone video call, mail, or email).
Disease status					X	X					X	
Survival/Vital Status		<----------									X	Upon Sponsor request, participants may be contacted for survival/vital status information at any time during the study.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Efficacy Procedures												
Tumor Imaging (CT of the Chest, CT or MRI of the Abdomen and Pelvis) [b]	X	<---------->			X[c]		X	X	X	X		See Section 8.2.1.2 for tumor imaging schedule details.
Safety Procedures												
Height and Weight	X	X	X	X	X							Height measured at Screening only.
Full Physical Examination	X				X							Within 7 days prior to C1D1.
Directed Physical Examination		X	X	X		X						A symptom-directed physical examination may be performed at any time during the study, as clinically indicated.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Vital Signs (resting BP, pulse rate, respiratory rate, temperature)	X	X	X	X	X	X						BP and pulse rate will be measured after the participant has been resting for 5 minutes.
12-lead ECG	X											Single 12-lead ECG after the participants has been recumbent for 5 minutes.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Upper endoscopy	X											Upper endoscopy at Screening is necessary for all cirrhotic participants only if more than 12 months have passed since the previous assessment. Participants without evidence of cirrhosis will not require an upper endoscopy to be eligible.
ECOG Performance Status	X	X	X	X	X	X						Within 7 days prior to C1D1. Thereafter, prior to dosing at treatment visits.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Child-Pugh score	X											Within 7 days prior to C1D1. Thereafter, only if any of the hepatic ECI criteria are met, document the Child-Pugh score with each visit until the hepatic ECIs resolve.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
AE/SAE Review	X	<----------										AEs: monitored up to 30 days after last dose. SAEs and pregnancy: monitored up to 90 and 120 days after last dose, respectively, or 30 days after last dose if participant starts a new anticancer therapy, whichever occurs first.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Laboratory Procedures (LOCAL laboratory)	**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.**											
Pregnancy Test – Serum or Urine (WOCBP only)		X	X	X	X	X	X					Refer to Appendix 5 for Contraception Guidance and Appendix 7 for country-specific requirements. Within 72 hours prior to each cycle of treatment and as required by local guidelines up to 120 days after last dose of study intervention or 30 days post dose if new anticancer treatment started, whichever comes first.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
PT/INR	X		X	X	X	X						Within 7 days prior to C1D1. Then, prior to every cycle starting with Cycle 2. Testing can be performed more frequently if the participant is receiving anti-coagulation medication.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
T3 (or Free T3), Free T4, and TSH	X		X	X	X							Within 7 days prior to C1D1. Then on Day 1 of every other cycle starting from Cycle 2 (eg, Cycle 2, 4, 6, 8, etc.) and at EOT. Free T3 is acceptable where T3 cannot be determined.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
AFP	X			X	X		<----------					AFP should be collected within 28 days prior to C1D1 and then on Day 1 of every 3 cycles starting from Screening (eg, Screening, Cycle 3, 6, 9, etc.) and at EOT. For participants who discontinue from study intervention prior to Cycle 17, AFP will be collected Q12W from the EOT Visit during the remainder of Year 1.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
												AFPs should be collected Q24W Years 2 to 5 and annually until Year 7 coinciding with imaging visits. Every effort should be made to collect samples at the same time of day. After Cycle 1, participants 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.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Hematology	X		X	X	X	X						Hematology and Chemistry to be collected within 7 days prior to C1D1 and then on Day 1 of every cycle. Urinalysis to be collected within 7 days prior to C1D1 and then on Day 1 of every other cycle starting from Cycle 2 (eg, Cycle 2, 4, 6, 8, etc.), at EOT and Safety Follow-up Visit. Every effort should be made to collect samples at the same time of day.
Chemistry Panel	X		X	X	X	X						
Urinalysis	X		X	X	X	X						

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Laboratory Procedures (CENTRAL laboratory)	**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.** Sponsor consultation is required prior to performing local hepatitis testing. Local hepatitis testing is acceptable, including during the screening period, provided lower limit of detection (LLOD) for HBV DNA Viral Load Test is at least 20 IU/mL or less. Refer to Section 8.11.1 for further details. Refer to Appendix 7 for country-specific requirements. Refer to Section 8.11.1 for repeat HBV and HCV testing during rescreening.											
HIV	X											Testing is not required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Anti-HCV (IgG)	X											
If Anti-HCV (IgG) positive:												If these conditions are met, HCV genotype and HCV viral load will be conducted within 28 days prior to study intervention.
HCV genotype	X											Participant may be randomized if results are pending and the participant meets all other eligibility criteria.
HCV viral load[d]	X											
Anti-HBc (total and IgM), anti-HBs, HBV viral load, HBsAg[d]	X											

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
If (1) HBsAg+ and/or detectable HBV viral load or (2) anti- HBc+, anti-HBs-, HBsAg- and viral load <100 IU/mL:												If these conditions are met, anti-HDV, anti-HBe and HBeAg will be conducted within 28 days prior to study intervention.
Anti-HDV	X											Participant may be randomized if results are pending and the participant meets all other eligibility criteria.
Anti-HBe and HBeAg[d]	X											Participant may be randomized if results are pending and the participant meets all other eligibility criteria.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
Biomarkers												
Tumor Tissue Sample	X											All participants who undergo surgical resection will be required to submit a tumor tissue sample during Screening. Formalin-fixed, paraffin-embedded block specimens are preferred to slides. Participants who undergo local ablation are encouraged to submit a tumor tissue sample during Screening if available. All participants are encouraged to submit surrounding non-tumor tissue during Screening if available.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
CCI [redacted]		X										Details for collection of CCI [redacted] can be found in Section 8.8.1 Planned Genetic Analysis Sample Collection.
CCI [redacted]		X	X	X	X							CCI [redacted] should be collected predose on Day 1 of Cycles 1, 2, 5 and at EOT.
CCI [redacted]		X	X	X	X							CCI [redacted] should be collected predose on Day 1 of Cycles 1, 2, 5 and at EOT.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
CCI [redacted]		X	X	X	X							CCI [redacted] should be collected predose on Day 1 of Cycles 1, 2, 5 and at EOT.
CCI [redacted]		X	X	X	X		<---------->					CCI [redacted] should be collected predose on Day 1 of Cycles 1, 2, 3, 5, 7, 9, 11, 13, 15, 17 and at EOT. CCI [redacted] should be collected Q24W Years 2 to 5 and annually until Year 7 coinciding with imaging visits.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
												For participants who discontinue from study intervention prior to Cycle 17, CCI [redacted] will be collected Q12W from the EOT Visit during the remainder of Year 1. During follow-up, if a clinic visit is not feasible, CCI [redacted] will not be collected.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	
[redacted] collection (optional)		X	X	X	X							Collection at home within 1 week prior to specified visit and brought into site on Day 1 of Cycles 1, 2, 5 and at EOT.
Patient-reported Outcomes												
EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-HCC18		X	X	X	X	X	<----------			---------->		Patient-reported outcomes (PROs) should be collected up to and including Year 5. See Section 4.2.1.3 for details regarding PROs. See Section 8.2.2 for timing and order of PROs at each visit.

Study Period	**Screening Phase**	**Intervention Phase (Every 3 Weeks and End After 17 Cycles of treatment)**			**End-of-Treatment**	**Post-Treatment Visits**						**Notes**
Treatment Cycle		1	2	3 and onwards (up to 17 cycles)	DC	Safety Follow-up[a]	Efficacy Follow-up Visits				Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Sections 8.11.2.1, 8.11.2.2, and 8.11.2.3
Scheduled Timing	-28 to -1				At time of DC	30 days post last dose	Q12W Year 1 from RAND	Q12W Year 2-3 from RAND	Q24W for Year 4-5 from RAND	Annually for Year 6-7 from RAND	~Q12W	
Window (days):		+3	±3	±3		+7	±7	±14	±14	±14	±14	

AE=adverse event; BCLC=Barcelona Clinic Liver Cancer; BP=blood pressure; C=Cycle; C1D1=Cycle 1 Day 1; CR=complete response; CT=computed tomography; CCI D=Day; DC=Discontinuation; ECG=electrocardiogram; ECI=Event of Clinical Interest; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EOT=End-of-Treatment; HCV=Hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; LLOD= lower limit of detection; MRI=magnetic resonance imaging; PD=progressive disease; PRO=Patient-reported Outcomes; PT=prothrombin time; Q3W=every 3 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; RAND = randomization; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

a. If the EOT Visit occurs ⩾30 days after the last dose of study intervention, a Safety Follow-up Visit is not required. In this situation, all procedures required at the Safety Follow-up Visit and EOT Visit are performed once and entered into the EOT Visit only.
b. Prior scans performed within the screening period, but before signing informed consent may be used if consistent with protocol requirements per Site Imaging Manual. The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the study to optimize the visualization of new tumor burden.
c. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to EOT Visit.
d. In the case of hepatic ECIs, additional tests are to be performed as described in Section 6.6.2, Guidance for Management of Hepatic Events of Clinical Interest. All additional laboratory tests should be performed by a central laboratory, if possible.

NOTE: For additional CCI, refer to Section 10.7.8 (Table 15).

2 INTRODUCTION

2.1 Study Rationale

HCC is one of the leading causes of cancer deaths worldwide. Furthermore, incidence and mortality rates are increasing in most parts of the world, including in the United States. Despite advances in early detection, liver transplantation, and liver-directed therapies, about 30% of HCC patients who present with early disease stage have potential curative options.

Surgical resection and local ablation are potentially curative strategies and are associated with 5-year survival rates of 60% to 80% (resection) and 40% to 70% (ablation) [Bruix, J. 2011] [European Association for the Study of the Liver 2012] [Mazzaferro, V., et al 2014] [Bruix, J., et al 2015] [Bruix, J., et al 2014]. However, tumor recurrence is common, and rates varies widely based on tumor features.

There is no standard of care in the adjuvant setting of HCC after these procedures. This population thus has an unmet medical need for adjuvant therapy with the goal of preventing disease recurrence and increasing survival by providing treatment with adjuvant pembrolizumab.

2.2 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (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 many indications. For more details on specific indications, refer to the Investigator's Brochure (IB).

2.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma (RCC). TILs can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated

T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (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 (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKC-θ), 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.

2.2.1.1 Hepatocellular Carcinoma: Epidemiology and Current Therapeutic Options

Hepatocellular carcinoma is one of the leading causes of cancer deaths worldwide and has one of the most rapidly rising mortality rates of any cancer in the USA. Most HCC arises in the setting of liver cirrhosis from varied causes, including viral hepatitis, excessive alcohol consumption, hemochromatosis, and metabolic syndrome [Dhanasekaran, R., et al 2012]. As a consequence of these different etiologies, HCC is a heterogeneous malignancy. Despite advances in early detection, in most regions only about 30% to 40% of HCC patients are diagnosed with very early and early-stage disease amenable to potential curative options like local ablation, resection, and liver transplantation [Park, J. W., et al 2015].

Current European Association for Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines recommend surgical resection as the primary treatment for a single HCC with Child-Pugh score A, normal serum bilirubin, and no clinically significant portal hypertension. The global BRIDGE study, a multiregional longitudinal cohort study including patients newly diagnosed with HCC, evaluated the survival rates based on the ideal resection status as defined in the EASL/AASLD guidelines [Roayaie, S., et al 2015]. The 3- and 5-year survival rates were 74% and 65%, respectively, for ideal resection candidates who were surgically removed, 55% and 55% for ideal resection candidates who were not surgically removed, and 47% and 35% for non-ideal resection candidates who were surgically removed; however, recurrence is common and surgical resection is associated with tumor recurrence rates of approximately 50% at 3 years and 70% at 5 years [Bruix, J. 2011] [European Association for the Study of the Liver 2012]

[Mazzaferro, V., et al 2014] [Lu, L. C., et al 2014] [Bruix, J., et al 2015] [Bruix, J., et al 2014].

Local ablation is also used to treat HCC and is associated with 5-year survival rates of 40% to 70% [European Association for the Study of the Liver 2012]. Several studies have evaluated the role of prognostic factors in patients undergoing local ablation. In a retrospective from China tumor size, number and AFP were reported to be important prognostic factors [Wang, T., et al 2016]. Another study from Japan also found these criteria to be significantly associated with RFS in a multivariate analysis [Takuma, Y., et al 2018]. Tumor size and number have been used as prognostic factors globally in treatment guidelines with variable thresholds across different regions [European Association for the Study of the Liver 2012] [Kudo, M. 2018] [Yau, T., et al 2014].

Thus, the prognosis after resection or ablation remains unsatisfactory, and prevention of recurrence with adjuvant treatments is an important unmet medical need in patients with HCC.

Currently, there is no standard of care in the adjuvant setting because no treatment has a proven to show a conclusive benefit in large, randomized studies in patients with HCC after potentially curative treatment [Bruix, J. 2011] [European Association for the Study of the Liver 2012] [Omata, M., et al 2010] [Verslype, C., et al 2012] [Kudo, M., et al 2011] [Zhuang, L., et al 2012]. Although interferon is the most widely studied treatment in this setting, evidence is conflicting based on studies with small sample sizes, heterogeneous patient populations, and differing types and length of treatment [Zhuang, L., et al 2012]. Studies of other potential adjuvant treatment options, such as vitamin K2, retinoids, and systemic chemotherapy, have also been inconclusive in terms of efficacy and safety [Lu, L. C., et al 2014] [Zhuang, L., et al 2012] [Okita, K., et al 2015] [Yoshida, H., et al 2011].

The oral multikinase inhibitor sorafenib is approved in patients with unresectable HCC based on 2 Phase 3 randomized studies [Cheng, A.-L., et al 2009] [Llovet, Josep M., et al 2008] and is one of the treatment options in patients with advanced HCC [Bruix, J. 2011] [European Association for the Study of the Liver 2012] [Omata, M., et al 2010] [Verslype, C., et al 2012] [Kudo, M., et al 2011]. Lenvatinib is another oral multikinase inhibitor approved for first-line treatment of unresectable HCC based on results from the open-label Phase 3 REFLECT study [Kudo, M., et al 2018]. The STORM study was designed to assess the efficacy and safety of sorafenib versus placebo as an adjuvant therapy in patients with HCC with a complete radiological response after curative treatment by surgical resection (R0 on pathological report) or local ablation (complete response by imaging techniques) [Bruix, J., et al 2015]. A total of 1114 patients were randomly assigned (1:1) to receive 400 mg oral sorafenib or placebo twice a day, for a maximum of 4 years. The primary outcome was RFS. With a median follow-up for RFS of 8.5 months (interquartile range [IQR] 2.9–19.5) in the sorafenib group and 8.4 months (IQR 2.9–19.8) in the placebo group, no difference in median RFS between the two groups (33.3 months in the sorafenib group versus 33.7 months in the placebo group; hazard ratio [HR] 0.940; 95% CI: 0.780–1.134; 1-sided p=0.26) was observed. The most common Grade 3 or 4 AEs were hand-foot skin reaction (154 [28%] of 559 patients in the sorafenib group versus 4 [<1%] of 548 patients in the placebo group) and diarrhea (36 [6%] versus 5 [<1%] in the placebo group). Based on these results, sorafenib

was found to be an ineffective intervention in the adjuvant setting for HCC after resection or ablation. A study from Japan evaluated the role of adoptive immunotherapy with autologous lymphocytes in the adjuvant setting. Though there was no statistically significant improvement in OS, significant improvement in RFS was noted, potentially supporting the role of immunotherapy in the adjuvant setting [Takayama, T., et al 2000]. Another study using brivanib as adjuvant therapy post-transarterial chemoembolization in patients with hepatocellular carcinoma was terminated early due to lack of efficacy in the advanced setting. Data with 502 enrolled patients and a median follow-up of approximately 16 months showed no improvement in OS with brivanib versus placebo (median, 26.4 vs. 26.1 months [HR]: 0.90 [95% CI: 0.66-1.23]) [Kudo, M., et al 2014].

Nivolumab is currently being evaluated in a Phase 3, randomized, double-blind study in patients with HCC at high risk of recurrence after curative hepatic resection or ablation.

2.2.2 Preclinical and Clinical Studies

Therapeutic studies in mouse models have shown that the administration of antibodies blocking the PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 and anti-mouse PD-L1 antibodies have showed antitumor responses as monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promotes CD8+ T-cell infiltration into the tumor and the presence of interferon-γ, granzyme B, and perforin, indicating that the mechanism of action involves local infiltration and activation of effector T-cell function in vivo [Ropponen, K. M., et al 1997] [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008] [Pölcher, M., et al 2010] [Okazaki, T., et al 2001] [Greenwald, R. J., et al 2005]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Clinical trials have showed efficacy using pembrolizumab in participants with advanced melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma. In addition, recent data show emerging evidence of single-agent activity in additional tumor types such as mesothelioma, urothelial cancer, ovarian cancer, neuroendocrine carcinoma, and small cell lung cancer.

In a mouse model of HCC, blockade of PD-1 with immune stimulatory monoclonal antibodies extended survival [Morales-Kastresana, A., et al 2013]. HCC patients with higher expression of tumoral PD-L1 had a significantly poorer prognosis than patients with lower expression, and tumor expression of PD-L1 has also been shown to be an independent predictor for postoperative recurrence in HCC patients [Gao, Q., et al 2009]. High expression levels of PD-1 on TILs and peripheral blood mononuclear cells (PBMCs) have also been correlated with a poor prognosis in HCC patients after surgical resection [Shi, F., et al 2011].

On 22-SEP-2017, the Food and Drug Administration (FDA) granted accelerated approval to nivolumab for the treatment of HCC in patients who have been previously treated with sorafenib. Approval was based on a 154-patient subgroup of CheckMate-040 (NCT 01658878), a Phase 1/2 study of the anti-PD-1 antibody, nivolumab, in participants with advanced HCC. The study showed an overall response rate (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.

On 09-NOV-2018, the FDA granted approval to pembrolizumab for the treatment of patients with HCC who have been previously treated with sorafenib. This approval is based on data from KEYNOTE-224, a Phase 2 single-agent study with pembrolizumab 200 mg IV Q3W among 104 patients with advanced HCC, previously treated with sorafenib. As of a data cutoff of 13-FEB-2018, an ORR of 17% (95% CI: 11-26) was recorded [Zhu, A. X., et al 2018]. A substantial number of objective responses (17%) were consistently observed across several risk factors associated with the prognosis of HCC, including hepatitis B virus and hepatitis C virus infections, and also in those whose disease progressed with or who were intolerant to sorafenib. Among the 18 patients who responded, there was 1 complete response and 17 partial responses. Forty-six patients had stable disease, 34 patients had progressive disease, and 6 patients were not evaluable. The median time-to-response was 2.1 months (IQR, 2.1-4.1) and the median duration of response was not reached (range, 3.1-14.6+ months). The median PFS was 4.9 months (95% CI: 3.4-7.2), and the 12-month PFS rate was 28% (95% CI: 19-37). The median OS was 12.9 months (95% CI: 9.7-15.5) and the 12-month OS rate was 54% (95% CI: 44-63). Twenty-four percent (n = 25) of patients experienced Grade 3 treatment-related AEs, with the most common being increased aspartate aminotransferase (AST) (7%), increased alanine aminotransferase (ALT) (4%), and fatigue (4%). There was 1 case of Grade 4 treatment-related hyperbilirubinemia, and 1 patient death associated with ulcerative esophagitis attributed to study intervention. Sponsor-assessed immune-mediated hepatitis occurred in three (3%) patients, but there were no reported cases of viral flares of hepatitis B virus or hepatitis C virus.

The Phase 3 2L HCC study (KEYNOTE-240) confirmed these findings, with an ORR of 18%, PFS HR of 0.78 (95% CI: 0.609-0.987) at the prespecified primary analysis, and OS HR of 0.78 (95% CI: 0.611-0.998) at final analysis [Finn, R. S., et al 2019]. The difference in OS between the placebo and pembrolizumab arms was 3.3 months, the largest seen among recent second-line trials. Although OS and PFS did not meet their statistical endpoints, the data showed a favorable risk-benefit profile, and no additional toxicity signals were seen in KEYNOTE-240 [Finn, R. S., et al 2019].

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.

The benefit-risk profile for pembrolizumab in an adjuvant HCC population is unknown since these participants have not been previously studied with pembrolizumab. The safety and efficacy data generated to date provide a favorable benefit/risk assessment for the continued use of pembrolizumab as a treatment for multiple indications including adjuvant and advanced/metastatic melanoma and advanced/metastatic NSCLC, head and neck carcinoma, urothelial tract cancer, RCC, adenocarcinoma of the stomach/gastroesophageal junction, cervical cancer and as an investigational medicinal product in participants with triple-negative breast cancer, colorectal cancer, hematologic malignancies, and other advanced solid tumors.

Recent results from EORTC1325/KEYNOTE-054 show that adjuvant pembrolizumab increases RFS in adult patients with Stage III melanoma compared with placebo (HR = 0.57; 98.4% CI: 0.43 to 0.74; $p<0.0001$) [Eggermont, A. M. M., et al 2018]. The safety profile of adjuvant pembrolizumab in this study is consistent with the established safety profile of pembrolizumab across treatment indications. The percentages of participants with an AE in the pembrolizumab and placebo groups were 93.3% and 90.2%, respectively, and the incidence of AEs was generally comparable between the 2 treatment groups (pembrolizumab versus placebo).

Based on pembrolizumab data from other indications and from data in advanced HCC patients treated with pembrolizumab as well as with other agents in the class, a favorable benefits-risk profile is anticipated. No unexpected risks have been reported in advanced HCC with other immune checkpoint inhibitors other than transient elevations in ALT and AST.

The existing data suggest that PD-1 blockade is an effective therapeutic strategy and the benefit/risk assessment for participants included in this study is considered to be favorable.

Participants in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine. However, experience with this drug approved in other indications, as well as with similar drugs in advanced HCC suggests that study participants may receive a clinical benefit.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In participants at least 18 years of age with hepatocellular carcinoma (HCC) and complete radiological response after surgical resection or local ablation:

Objectives	Endpoints
Primary	
Objective: To compare recurrence-free Survival (RFS). Hypothesis (H1): Pembrolizumab is superior to placebo with respect to RFS as assessed by blinded independent central review (BICR).	RFS: the time from randomization to first documentation of disease recurrence (local, regional, or distant) as assessed by BICR or by pathology consistent with HCC, or death due to any cause (both cancer and non-cancer causes of death), whichever occurs first.
Objective: To compare overall survival (OS). Hypothesis (H2): Pembrolizumab is superior to placebo with respect to OS.	OS: The time from randomization to death due to any cause.
Secondary	
Objective: To evaluate the safety and tolerability.	Adverse events (AEs). Study intervention discontinuation due to AEs.
Objective: To compare score change from baseline in global quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health status/QoL scale and EORTC QLQ-HCC18.	Scores from the global health status/ quality of life (QoL) scale on the EORTC QLQ-C30 and EORTC QLQ-HCC18.
Objective: To characterize health utilities using the EuroQoL-5 Dimension Questionnaire, 5-Level (EQ-5D-5L) healthy utility scores.	EQ-5D-5L health utility score.

Objectives	Endpoints
Tertiary/Exploratory	

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4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multicenter, double-blind Phase 3 study of adjuvant pembrolizumab versus placebo in participants 18 years of age and older with complete radiological response after surgical resection or local ablation. Staging of participants with complete radiological response after surgical resection will be defined per American Joint Committee on Cancer (AJCC) 8th Edition (Appendix 10) with adaptations based on tumor characteristics as established by the pathology report.

Study population will include participants with complete radiological response after surgical resection (R0 resection) of HCC and intermediate, high, or very high risk of recurrence and participants with complete radiological response after local ablation of HCC and intermediate or high risk of recurrence.

The intermediate risk of recurrence population will be capped at approximately 20% of all participants enrolled in the study.

Participants may be listed for liver transplantation in the status NT (not transplantable) during the course of the study. The risks of solid organ transplant after treatment with PD-1 inhibitor therapy have not been extensively studied. The timeframe for safe or appropriate solid organ transplantation after the last dose of pembrolizumab is unknown. Therefore, it is recommended not to perform solid organ transplantation within at least 120 days (5 half-

lives) of stopping pembrolizumab. The risks and benefits of transplant should be discussed with the participant by the treating investigator.

The Asia population [not including Japan] may be up to approximately 60% of the total study population.

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Investigators will assess disease recurrence radiographically (with site radiologist) during study intervention and efficacy follow-up. Disease recurrence will be documented by the investigator radiographically (with site radiologist) and will be verified by BICR prior to discontinuation of study intervention. Disease recurrence can also be confirmed with pathology if required per the site's standard of care. For participants who discontinue for reasons other than BICR-verified extrahepatic disease recurrence or confirmed with pathology if required per the site's standard of care, imaging should continue to be performed as if on study intervention until extrahepatic disease recurrence has either been verified by BICR or confirmed with pathology if required per the site's standard of care.

Disease recurrence can be intrahepatic or extrahepatic:

- Intrahepatic disease recurrence will be defined as the appearance of one or more intrahepatic lesions with a longest diameter of at least 10 mm and a typical vascular pattern of HCC on triphasic CT scan or MRI of the abdomen (ie, hypervascularization in the arterial phase with washout in the portal venous or late venous phase). Intrahepatic lesions larger than 10 mm that do not show a typical vascular pattern may be diagnosed as HCC by evidence of a growth interval of at least 10 mm in ≥4 weeks after the initial scan showing disease recurrence. Both de novo liver tumors and intrahepatic metastases will be considered intrahepatic disease recurrence.

- Extrahepatic disease recurrence will be defined as the appearance of one or more unequivocal new extra-nodal lesions or malignant enlargement of a previously normal lymph node. If a potential new extra-nodal lesion is equivocal, for example because of small size or clinical presentation, continued follow-up will show whether it truly represents disease recurrence. If it is later confirmed as disease recurrence, it should be retrospectively assigned at the visit where it was first seen. A lymph node ≥15 mm in short axis is presumed to represent disease recurrence. A lymph node 10-14 mm in short axis may represent disease recurrence, with reviewers using additional information (such as location, morphological signs and change in size) to inform their clinical judgment to determine whether it represents disease recurrence. Participants will also be discontinued from study intervention if they have ascites or pleural effusion deemed to be malignant.

Participants may be unblinded after BICR-verified disease recurrence at the investigator discretion upon Sponsor consultation only if this information is required to guide future treatment decisions.

If participant is unblinded, the circumstances around the unblinding (eg, date and reason) must be documented promptly. Only the principal investigator or delegate and the respective subject's code should be unblinded. Sponsor personnel directly associated with the conduct of the study should not be unblinded.

Follow-up visits and imaging schedules will be scheduled per the SoA (Section 1.3).

The primary endpoints of the study are RFS by BICR and OS. This study will also examine the safety and tolerability of pembrolizumab versus placebo administered Q3W for 17 cycles and PROs as secondary endpoints. Safety evaluations will include AE monitoring, physical examinations, clinical laboratory parameters (hematology and chemistry), vital signs, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status (see Appendix 9). AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Patient-reported outcomes (PROs) are secondary endpoints evaluating any clinically relevant differences between the two treatment arms in global QoL.

This study will be conducted in conformance with Good Clinical Practices.

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Results of the interim analyses will be reviewed by an external Data Monitoring Committee (eDMC), which will make recommendations to the Sponsor to continue, modify, or end the study according to the plan described briefly in Section 4.4.1 and in detail in Section 9.

The study will be considered a success if superiority in RFS is established.

NOTE: Country-specific protocol operational items are described in Appendix 7.

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

4.2 Scientific Rationale for Study Design

This Phase 3 study is designed to evaluate the efficacy and safety of pembrolizumab as adjuvant treatment in adult patients with HCC and complete radiological response after surgical resection or complete radiological response after local ablation. Treatment will be double-blinded. At the time of the study start, there are no anti-PD-1 agents approved for first-line HCC, underscoring the high unmet need for treatment of this disease, and the rationale for not allowing crossover. There is no established standard of care in the HCC adjuvant setting. Rationale for the use of a placebo as a comparator is described in Section 4.2.2. One year of adjuvant treatment is consistent with other studies evaluating pembrolizumab in the adjuvant setting in different tumor types, including melanoma, NSCLC, and RCC.

The study will be considered a success if superiority in RFS is established at either an interim analysis or the final analysis under multiplicity control as detailed in Section 9.8. The OS hypothesis will be tested only if RFS null hypothesis is rejected.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will have 2 primary endpoints: RFS and OS.

RFS will be based on disease recurrence (local, regional, or distant) as assessed by BICR. RFS 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.

RFS has been used as the primary outcome measure in many Phase 3 studies assessing anti-PD-1 therapy in the setting of Stage III adjuvant melanoma, including S1404/KN053, EORTC1325/KN054, CheckMate 238, and COMBI-AD [Eggermont, A. M. M., et al 2018] [Weber, J., et al 2017] [Long, G. V., et al 2017]. RFS has also showed to be a valid surrogate endpoint to OS for adjuvant randomized studies assessing checkpoint inhibitors in high risk melanoma after surgical resection [Suciu, S., et al 2018].

Expedited verification of absence of radiologic evidence of disease will be performed by BICR at Screening and will be used to determine participant eligibility. Disease recurrence will be documented by investigator radiographically (with site radiologist) and will be verified by BICR. Disease recurrence can also be confirmed by pathology if required per the site's standard of care.

BICR has been advocated to control bias in randomized clinical trials that might result from errors in recurrence assessments. Bias may be introduced by the potentially subjective

components of imaging endpoint assessment. While important efforts both to minimize subjectivity and to improve consistency of radiologic endpoint assessment have been made [Therasse, P., et al 2000] [Miller, A. B., et al 1981], endpoint evaluation still depends to some extent on the individual reviewing the image and the time point at which s/he reviews it. BICR is one strategy to reduce the potential for this bias.

OS (the time from randomization to death due to any cause) after administration of pembrolizumab versus placebo will also be a primary endpoint in this study. This endpoint is precise and easy to measure, documented by the date of death. Bias is not a factor in OS measurement. Survival improvement should be analyzed as a risk-benefit analysis to assess clinical benefit [US Department of Health and Human Services and Food and Drug Adm 2005].

Overall survival (OS) has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. Overall survival is also considered the gold standard primary endpoint for studies of adjuvant treatments for cancer. However, OS can be extensively influenced by the effects of the subsequent oncologic therapies for the treatment of HCC. Thus, both RFS and OS are included as primary endpoints. The study will be considered a success if superiority in RFS is established.

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4.2.1.2 Safety Endpoints

Safety is a secondary endpoint in this study.

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, HCC-specific] 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 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.3.3 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.

4.2.1.4 Pharmacokinetic Endpoints

No pharmacokinetic endpoints are planned for this study.

4.2.1.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.1.6 Planned Exploratory Biomarker Research

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

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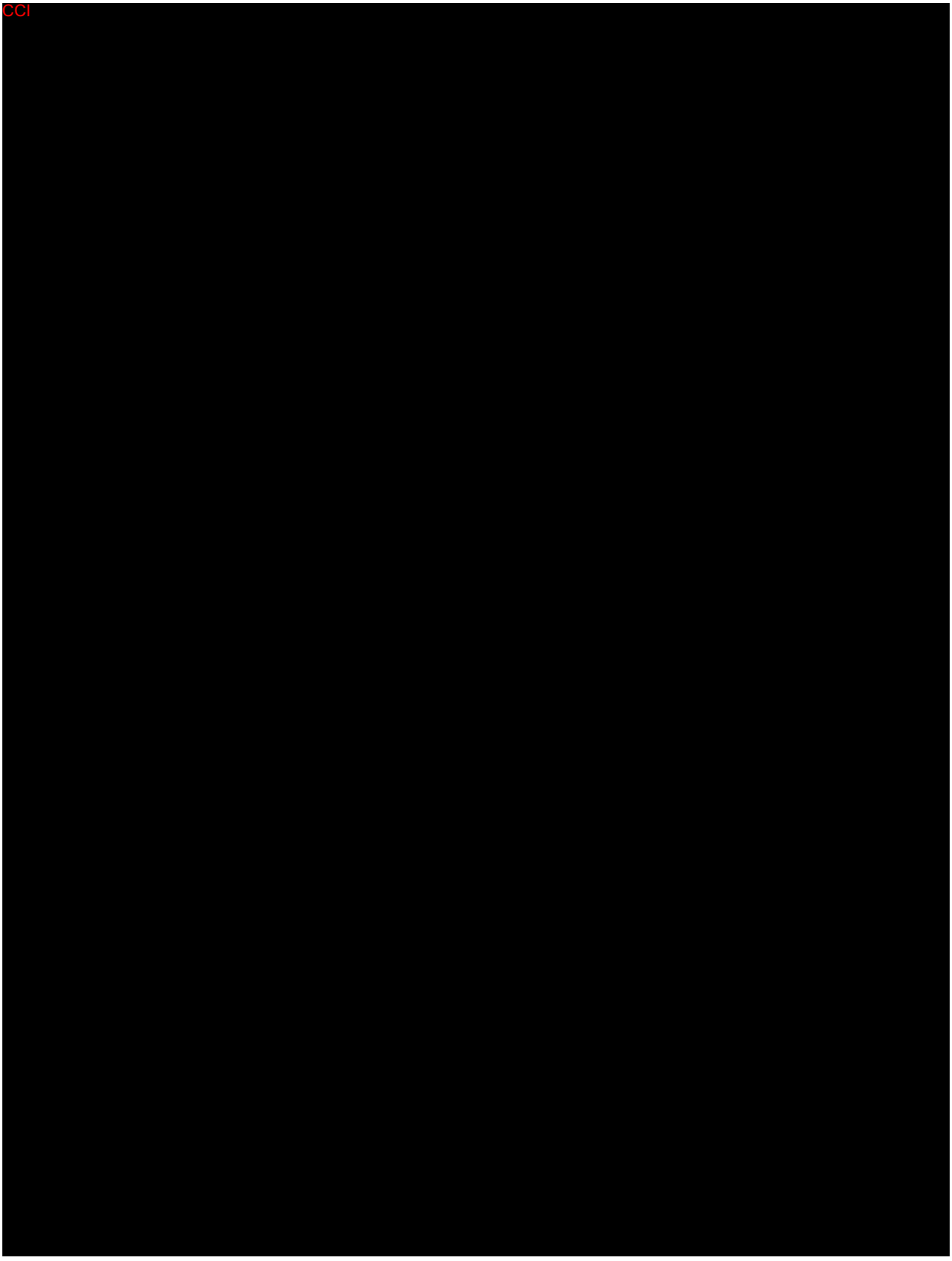

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4.2.2 Rationale for the Use of Comparator/Placebo

In this study, participants will be randomized at enrollment to the pembrolizumab or placebo intervention groups and are expected to be treated for 17 administrations (approximately 1 year). Placebo will be normal saline solution prepared by the local unblinded pharmacist, dosed and administered in the same manner as the investigational product. There is no established standard of care in the HCC adjuvant setting. In randomized clinical trials, for conditions having no effective treatment, a placebo control in which the new treatment is compared, is warranted. Placebo is being used as a control to allow for a blinded study, thereby limiting bias and providing a control arm that is consistent with standard of care for patients with HCC and complete radiological response after surgical resection or local ablation.

4.3 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from 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.

4.3.1 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W for 17 administrations (approximately 1 year).

4.4 Beginning and End of Study Definition

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

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

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

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

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

1. Has a diagnosis of HCC documented radiologically by AASLD criteria (participants undergoing ablation without a prior biopsy; see Appendix 12) and/or pathologically (participants undergoing ablation and not meeting AASLD criteria, and participants undergoing surgical resection); fibrolamellar, sarcomatoid and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible and:

    A. Has a complete radiological response after surgical resection (R0 resection) and an intermediate risk (Stage I), high risk (Stage II, IIIA) or very high risk of recurrence (subtypes of Stage IIIB as described below) as per American Joint Committee on Cancer (AJCC) 8th edition with adaptations based on tumor characteristics as established by the pathology report.

        - Intermediate risk of recurrence: solitary tumor ≥2 cm without microvascular invasion and not histologic Grade 3 or 4.

- High risk of recurrence: solitary tumor ≥2 cm with microvascular invasion or same size and histologic Grade 3 or 4, or multiple tumors, regardless of microvascular invasion or histologic grade.

- Very high risk of recurrence: single tumor or multiple tumors of any size with macrovascular invasion. Stage IIIB tumor(s) with direct invasion of adjacent organs or with perforation of visceral peritoneum will not be eligible.

Note: HCC diagnosis and presence of microvascular invasion (where applicable as noted above) and histologic grade will be centrally confirmed prior to enrollment. If there is a discrepancy between local and central pathology results, results from the central review will be used to determine eligibility.

OR

B. Has a complete radiological response after local ablation (only radiofrequency or microwave ablation are allowed) and intermediate, high risk of recurrence or very high risk group.

- Intermediate risk of recurrence: Solitary tumor ≥2 cm and ≤3 cm.

- High risk of recurrence: 2-4 tumors, with all ≤3 cm or one solitary tumor >3 cm and ≤5 cm.

- Very high risk group: 2-4 tumors with at least one >3 cm and all ≤5 cm.

Note: If AFP determined at Screening is ≥100 ng/mL, the participant in intermediate risk group will be upstaged to the high risk of recurrence group, regardless of tumor size or number of tumors present.

Note: Local ablation can be performed in 1-2 procedures to treat the initial diagnosis of HCC. If 2 procedures are performed, randomization needs to occur within 12 weeks of the date of the first local ablation.

Note: For all participants, measurement of the tumor(s) will be based on the longest diameter of the lesion(s). Include participants with first recurrence of HCC and prior resection/ablation at least 2 years from the current diagnosis, after discussion with the Sponsor.

Note: For all participants, the number of lesions counted toward risk categorization should meet diagnostic criteria for HCC either by imaging (AASLD) and/or pathology confirmation.

2. No more than 12 weeks must have elapsed between the date of the staging and the date of surgical resection or local ablation.

   Note: Initial staging CT scan or MRI should be submitted to the iCRO but is not required prior to enrollment.

   Note: For participants referred for treatment, the staging must be completed prior to resection or local ablation. This staging must be based on radiologic and pathologic information available. A second scan may be performed for staging. If more than one scans are performed, the most recent scan meeting protocol requirements should be used.

3. Has an eligibility scan (CT of the chest, triphasic CT scan or MRI of the abdomen, and CT or MRI of the pelvis) confirming complete radiological response ≥4 weeks after complete surgical resection or local ablation. Randomization needs to occur within 12 weeks of the date of surgical resection or local ablation.

   Note: A maximum of 2 additional weeks is allowed when needed, and reason(s) must be documented in source documents.

   Note: Complete radiological response (also called “complete radiological necrosis”) is defined as the absence of enhancing tissue at the tumor site by triphasic CT scan or MRI of the abdomen.

   Note: Participants who after surgical resection or local ablation have radiologic evidence of a suspicious lesion that does not meet the diagnostic criteria for HCC, a second scan can be performed at least 4 weeks later and assessment of changes in size and vascularity will be used to determine eligibility by BICR.

4. Has no radiologic evidence of disease prior to enrollment as per investigator assessment.

   Note: After the investigator determines absence of radiologic disease, expedited verification of absence of radiologic evidence of disease will be performed by BICR at Screening and will be used to determine participant eligibility.

5. Has an ECOG performance status of 0 or 1 within 7 days prior to C1D1 (Appendix 9).

6. Has a Child-Pugh class A liver score (5 to 6 points) within 7 days prior to C1D1 (see Section 8.3.4).

7. Has AFP concentration lower than 400 ng/mL within 28 days prior to C1D1 (if there are several AFP values available within 28 days before C1D1, the closest AFP value to C1D1 should be below 400 ng/mL).

8. Has AFP concentration at initial diagnosis prior to resection or ablation available (if there are several AFP values available prior to resection or ablation, the closest AFP value to the date of resection or ablation should be entered in the eCRF).

   Note: Participants without AFP concentration at initial diagnosis prior to resection or local ablation may be allowed to be randomized upon Sponsor consultation.

9. Participant may have a past or ongoing HCV infection. Participants must have completed their treatment at least 1 month prior to C1D1 or have received at least 1 month of DAA HCV therapy with no DAA-related safety events and stable LFTs. For participants not on anti-HCV therapy at the time of randomization, DAAs for treatment of HCV infection can be initiated per Investigator's discretion, if LFTs are stable after 3-6 months of study intervention upon Sponsor consultation. Refer to Appendix 7 for country-specific requirements.

10. Participant may have controlled hepatitis B, as long as they meet the following criteria:

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   Refer to Appendix 13 for hepatitis B definitions and treatment considerations.

11. Has recovered adequately from toxicity and/or complications from the local intervention (surgical resection or local ablation) prior to starting study intervention.

Demographics

12. Is male or female, at least 18 years of age at the time of signing the informed consent.

Female Participants

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

    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), 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 corresponding to the time needed to eliminate any study intervention(s) after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours before the first dose of study intervention.

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

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 5.

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

Informed Consent

14. Participant (or legally acceptable representative if applicable) has provided documented informed consent/assent for the study and agrees to RFS, CCI [redacted], and OS data collection until the study endpoints are reached. The participant may also provide consent/assent for future biomedical research; however, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

15. All participants who undergo surgical resection will be required to submit a tumor tissue sample during Screening. Participants who undergo local ablation are encouraged to submit a tumor tissue sample during Screening if available. All participants are encouraged to submit surrounding non-tumor tissue during Screening if available.

    Note: For participants who undergo surgical resection, tumor tissue sample can be submitted from the surgical resection specimen itself. For participants who undergo local ablation, if tumor tissue is submitted it should ideally be obtained prior to or during the local ablation procedure.

16. Has adequate organ function as defined in the following table (Table 2). Specimens must be collected within 7 days prior to C1D1.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥60,000/µL
Hemoglobin	≥8.0 g/dL[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤2 mg/dL OR direct bilirubin ≤ULN for participants with total bilirubin levels >2 mg/dL
AST (SGOT) and ALT (SGPT)	≤5 × ULN
Albumin[c]	>3.0 g/dL
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT is within therapeutic range of intended use of anticoagulants

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

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

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

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

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

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a known additional malignancy that is progressing or has required active antineoplastic treatment (including hormonal) or surgical procedure 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.

2. Has had esophageal or gastric variceal bleeding within the last 6 months. All cirrhotic participants will be screened for esophageal varices with an upper endoscopy, unless such assessment has been performed in the past 12 months before C1D1. If varices are present, they should be treated according to institutional standards before starting study intervention.

   Note: Participants without evidence of cirrhosis will not require an upper endoscopy to be eligible.

3. Has clinically apparent ascites on physical examination.

4. Has had clinically diagnosed hepatic encephalopathy in the last 6 months. Participants on rifaximin or lactulose to control their hepatic encephalopathy regardless of when the diagnosis of hepatic encephalopathy occurred are not eligible.

5. Has received local therapy to liver, ablation other than with radiofrequency or microwave ablation (ie, alcohol ablation, transcatheter chemoembolization [TACE], transcatheter embolization [TAE], hepatic arterial infusion [HAI], local radiation/Stereotactic Body Radiation Therapy [SBRT] or radioembolization).

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

7. Has an active infection requiring systemic therapy.

8. CCI [redacted]

9. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

10. Has known active tuberculosis (TB; *Bacillus* tuberculosis).

Prior/Concomitant Therapy

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

12. Has received prior systemic anticancer therapy for HCC including investigational agents.

13. Is receiving any of the following prohibited concomitant therapies (see Section 6.5):

    - Antineoplastic systemic chemotherapy or biological therapy.
    - Immunotherapy not specified in this protocol.

- Investigational agents other than pembrolizumab.

- Received prior radiotherapy within 2 weeks of start of study intervention.
  Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2weeks of radiotherapy) to non-CNS disease.

- Oncological surgical therapy.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. Inhaled or topical steroids are allowed, and systemic steroids at doses ≤10 mg/day prednisone or equivalent are allowed. Exception: steroids may be used for premedication prior to imaging.

14. 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®, [Influenza Vaccine Live, AstraZeneca]) are live attenuated vaccines and are not allowed.
    Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

15. 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 C1D1.

    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

16. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to C1D1.

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

18. 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).
    Note: 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.

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

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

Other Exclusions

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

5.3 Lifestyle Considerations

5.3.1 Contraception

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

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.2 Pregnancy

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

5.3.3 Use in Nursing Women

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently 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 consent will not be replaced.

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experi-mental	Pembrolizumab	Drug	Vial	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle	Test Product	IMP	Centrally by Sponsor
Arm 2	Placebo Comparator	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

EEA=European Economic Area; IMP = investigational medicinal product; IV = intravenous; 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.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

CCI

6.3.3 Blinding

A double-blinding technique will be used. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Administration of study medication(s) will be monitored by the investigator and/or study staff. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol-specified treatment plan for more than 12 weeks between pembrolizumab doses for nondrug-related or administrative reasons require consultation

between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

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

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

6.5 Concomitant Therapy

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

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab.
- Radiation therapy.
- Oncologic surgical therapy.
- Live vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Refer to Appendix 7 for country-specific requirements.
  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids except when used for the following purposes.
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - To premedicate for IV contrast allergies
    - To treat COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
    - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease
- DAA HCV therapy with potential drug interactions with study intervention that need to be continued post-randomization.

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 Screening and Treatment Phase of this study. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nih.gov website.

Listed below are examples known hepatotoxic drugs that should be avoided:

Etifoxine

Isoniazid

Nitrofurantoin

Ketoconazole

Amiodarone

Phenytoin

Herbal supplements or alternative medicines should also be avoided during the Screening and Treatment Phase of this study.

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

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

6.5.1 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 6.6.1, Table 4. 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 4 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

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

Refer to Appendix 7 for country-specific requirements.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 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 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Non-hepatic 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 anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		
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 5.

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

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

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 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.

6.6.2 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 if HECI:

All Participants

- All participants should be considered for evaluation according to the directions below within 72 hours of the alert for a non-overdose 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, glutamyl transpeptidase, international normalized ratio (INR), and complete blood count with differential

    - Measure HCV RNA viral load

    - HBV DNA, HbsAg, HbeAg, anti-HBc (total and IgM), anti-Hbe, and anti-HBs regardless of prior HBV status (Note: participants should be questioned about compliance with the use of antiviral agents)

    - Other laboratories or imaging studies as clinically indicated

    - Consider liver biopsy if indicated

HCC patients are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in approximately 1% of participants who received pembrolizumab. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC participants in this study.

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 laboratory test results 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 viral load (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.
Hepatitis C exacerbation in participants with HCV RNA positive	Rapid elevation of ALT to >5×ULN and/or >3× 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 viral load to rule out new infection. Measure safety laboratory test results for AST, ALT, ALP, T Bili, D Bili, and INR on **weekly** basis Measure HCV viral load **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 re-occurs with rechallenge	Interrupt pembrolizumab/placebo study intervention 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.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

The 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). If 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/vaccination will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 (SoA) and Section 8.11.3 (Participants Discontinued from Study Intervention but Continuing to be Monitored in the Study) unless the participant has withdrawn from the study (Section 7.2).

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

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

The participant or participant's legally acceptable representative requests to discontinue study intervention

AEs described in the dose modification table that require discontinuation of study intervention (refer to Section 6.6.1).

After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor.

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

The participant has a confirmed positive serum pregnancy test.

The participant is receiving any prohibited concomitant medication requiring withdrawal (refer to Section 6.5).

Participant has any of the following non-overdose hepatic ECIs:

- ALT >20 ×ULN (confirmed within 1 week)
- Drug-related total bilirubin >10 × ULN
- CP score of >9 points
- Hepatic encephalopathy
- If ascites is not manageable by intervention within 3 days
- Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)

Recurrence of either intrahepatic or extrahepatic disease.

Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment

Completion of 17 treatments (approximately 1 year) with pembrolizumab versus placebo.

Note: The number of treatments is calculated starting with the first dose.

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.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

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

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

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

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

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

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

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical/surgical history will be obtained by the investigator or qualified designee. The medical/surgical history will collect all active conditions (including smoking and alcohol use) and any condition diagnosed within the prior 10 years that the investigator considers to

be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history. Participant demography information will be collected during the Screening Phase. Demography information includes date of birth (or age), sex, race/ethnicity.

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before C1D1. Prior medications for hepatitis B and C and their outcome should also be recorded. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 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. Record concomitant medications beyond 30 days after treatment discontinuation if related to SAE or ECI.

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 8.11.1.

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.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff and/or qualified designee according to the specifications within the Pharmacy Manual. Study intervention should begin within 3 days of randomization. Exceptionally, randomization can occur within 5 days prior to C1D1 upon discussion with the Sponsor.

8.1.8.1 Timing of Dose Administration

Pembrolizumab/placebo will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of 5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes –5 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 as outlined in the SoA and Section 8.11.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study 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.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

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

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

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

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

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

In addition to survival, efficacy will be assessed based on imaging evaluation of changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for image collection and transmission to the iCRO 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. Magnetic resonance imaging is the strongly preferred modality for imaging the brain, if clinically indicated. The same imaging technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on imaging.

Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

All scheduled images for all study participants from the sites will be submitted to the iCRO. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease recurrence, as well as imaging obtained for other reasons, but which show radiologic recurrence, should also be submitted to the iCRO. After the investigator determines absence of radiologic disease, expedited verification of absence of radiologic evidence of disease will be performed by BICR at Screening and will be used to determine participant eligibility.

When the investigator identifies radiographic recurrence, the iCRO will perform expedited verification of radiologic recurrence by BICR and communicate the results to the study site and Sponsor via email. Imaging should continue until disease recurrence has been verified by BICR (see Section 8.2.1.2). All scans must be submitted to the iCRO until extrahepatic disease recurrence has been verified by BICR. Once extrahepatic disease recurrence has been verified centrally, subsequent imaging (if acquired) should not be submitted to the iCRO.

Participants should continue treatment or continue in the Efficacy Follow-up Phase until disease recurrence has been verified by BICR or confirmed with pathology if required per the site's standard of care. Exceptionally, if the investigator identifies disease recurrence that is not verified by BICR and the participant is clinically unstable or unable to continue study intervention due to rapid clinical deterioration, study intervention or continue in the Efficacy Follow-up Phase may be discontinued after consultation with the Sponsor.

Clinical instability is defined as the following:

- Symptoms and signs indicating clinically significant progression of disease
- Decline in ECOG performance status

- Requirements for intensified management, including increased analgesia, radiation or other palliative care

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to randomization. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to randomization. Expedited verification of absence of radiologic evidence of disease will be performed by BICR at Screening and will be used to determine participant's eligibility.

Tumor imaging at baseline includes the following:

- CT of the chest

- Triphasic CT (preferred) or MRI of the abdomen and pelvis

8.2.1.2 Tumor Imaging During the Study

The first on study imaging assessment should be performed at 12 weeks (±7 days) from the date of randomization. Imaging should be performed Q12W until Week 228 (±14 days) (~Year 4), Q24W thereafter until Week 260 (±14 days) (~Year 5), and annually thereafter for up to 2 years (~Year 7) or until any initial recurrence (intrahepatic or extrahepatic), whichever occurs first. Follow the schedule below after initial recurrence based on intra-hepatic or extra-hepatic recurrence. Recurrence should be BICR-verified or confirmed with pathology if required per the site's standard of care.

- If BICR-verified intrahepatic recurrence with absence of extra-hepatic recurrence, tumor imaging should be performed Q24W thereafter until Week 260 (±14 days) (~Year 5), and annually thereafter for up to 2 years (~Year 7), until extra-hepatic disease recurrence is documented radiographically by the investigator (with site radiologist) and verified by BICR. Disease recurrence can also be confirmed with pathology if required per the site's standard of care.

- Imaging should be discontinued after extra-hepatic recurrence that is verified by BICR. Disease recurrence can also be confirmed with pathology if required per the site's standard of care.

Imaging timing should follow calendar days from randomization and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until extra-hepatic disease recurrence is identified by the Investigator and verified by BICR or confirmed with pathology if required per the site's standard of care, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

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 DC study intervention for reasons other than BICR-verified disease recurrence or BICR-verified intra-hepatic recurrence, imaging should continue to be performed as if on study (see Sec. 8.2.1.2) until extra-hepatic disease recurrence is verified by BICR, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

NOTE: Participants who do not have confirmed extrahepatic recurrence, but decline study-specific imaging in Efficacy Follow-Up and move to Survival-Follow Up Phase, should be encouraged to submit imaging performed as standard of care (even retrospectively) in the Survival-Follow Up Phase.

8.2.2 Patient-reported Outcomes

The EQ-5D-5L and EORTC QLQ-C30, and EORTC QLQ-HCC18 questionnaires will be administered by trained site personnel and completed by participants in the following order: EQ-5D-5L first, then EORTC QLQ-C30, then EORTC QLQ-HCC18. The questionnaires should be administered prior to dosing on Day 1 of each cycle from Cycle 1-10 both inclusive, then on Day 1 of Cycle 12, 14, 16, at EOT, and at the 30-day Safety Follow-up Visit. For participants who discontinue from study intervention prior to Cycle 17, PROs will be collected Q12W from the EOT Visit during the remainder of Year 1. After Year 1, PROs are to be performed Q24W to align with imaging visits. After Year 2, PROs are to be performed Q24W to align with imaging visits, up to and including Week 216. PROs are collected again at Week 228, and Week 252 PROs should be collected up to and including Year 5 (Week 252).

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

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 Screening to End-of-Treatment), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height will be measured at Screening only. Weight will be measured per Section 1.3.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period within 7 days prior to C1D1. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses, ascites, and evidence of encephalopathy.

8.3.1.2 Directed Physical Examination

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

Investigators should pay special attention to clinical signs related to previous serious illnesses, ascites, and encephalopathy.

8.3.2 Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.3.3 Electrocardiograms

Single 12-lead electrocardiogram (ECG) will be obtained after participant has been recumbent for 5 minutes and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

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

8.3.4 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, total bilirubin level, serum albumin, and coagulation parameters [INR or PT]) and 2 of which are based on clinical assessment (ie, degree of ascites and degree of hepatic encephalopathy; see Appendix 14). The investigator or qualified designee will determine the Child-Pugh score during the Screening period within 7 days prior to C1D1 and thereafter as outlined in the SoA.

8.3.5 Clinical Safety Laboratory Assessments

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

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

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

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

For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every

attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

8.3.5.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

8.3.5.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of the C1D1 and thereafter as outlined in the SoA. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study intervention in the event of a positive test result. Refer to Appendix 7 for country-specific requirements.

8.3.6 Performance Assessments

8.3.6.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 9) at screening within 7 days prior to C1D1, prior to the administration of each dose of study intervention, at EOT and during the follow-up period as specified in the SoA (Section 1.3).

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

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

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

All AEs from the time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

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

All pregnancies and exposure during breastfeeding, from the time of intervention 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 must be reported by the investigator.

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 6.

Table 6 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of 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 9.4.1.

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

The Sponsor will 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. For guidance related to the diagnosis and management of hepatic ECIs, refer to Section 6.6.2.

- 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

- Gastrointestinal bleeding

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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

PK parameters will not be evaluated in this study.

8.6.1 CCI [redacted]

Blood should be collected predose for Cycles 1, 2, 5 and at EOT. CCI [redacted].

Further details are provided in the Laboratory Manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

CCI [redacted]

CCI

8.8.1 CCI

CCI

8.9 Future Biomedical Research Sample Collection

CCI

8.10 Health Economics 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:

- Number and duration of medical care encounters, including surgical procedures, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

8.11 Visit Requirements

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

8.11.1 Screening

Documented informed consent must be 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 C1D1. Exceptions are hepatitis testing and AFP, which may be conducted up to 28 days prior to C1D1. Refer to Appendix 7 for country-specific requirements.

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

For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to C1D1. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

All participants who undergo surgical resection will be required to submit a tumor tissue sample during Screening. Participants who undergo local ablation are encouraged to submit a tumor tissue sample during Screening if available. All participants are encouraged to submit surrounding non-tumor tissue 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.

For repeat HBV and HCV testing during rescreening, the site may proceed with randomization in certain cases after collecting hepatitis blood samples, but before results are available only with approval by Sponsor.

Sponsor consultation is required prior to performing local hepatitis testing. Local hepatitis testing is acceptable, including during the screening period, provided lower limit of detection (LLOD) for HBV DNA Viral Load Test is at least 20 IU/mL or less. If hepatitis testing is performed locally, site should report hepatitis tests result in electronic data collection (EDC) prior to randomization.

8.11.2 Treatment Period

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

8.11.2.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

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

8.11.2.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than BICR-verified extrahepatic disease recurrence will move into the Efficacy Follow-up Phase and tumor imaging should continue to be performed as if on study intervention (see Section 8.2.1.2), until extrahepatic disease recurrence is documented radiographically by the investigator (with site radiologist) and verified by BICR. Pathology may also be used to confirm disease recurrence if required per the site's standard of care.

Every effort should be made to collect information regarding disease status, the start of new anticancer therapy, disease recurrence, death or end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Follow-up Phase.

8.11.2.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first. Participants with initial recurrence as intrahepatic recurrence will continue imaging as detailed in Sections 8.2.1.1 and 8.2.1.2 and efficacy follow-up until extrahepatic disease recurrence after which they will move into the Survival Follow-up Phase.

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

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

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

8.11.3 Participants Discontinued from Study Intervention but Continuing to be Monitored in the Study

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final visit should be performed at the time of discontinuation. Any adverse events that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 10.3.5– Recording AE and SAE.

8.11.4 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. This excludes participants that have a previously recorded death event in the collection tool.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in 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 PROs) will be documented in an sSAP or separate analysis plans.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3 Double-blinded, Two-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) versus Placebo as Adjuvant Therapy in Participants with Hepatocellular Carcinoma and Complete Radiological Response after Surgical Resection or Local Ablation.
Treatment Assignment	Participants will be randomized in a 1:1 ratio to receive pembrolizumab or placebo. This is a double-blind study. Treatment allocation/randomization will be CCI [redacted] • CCI [redacted]
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All-Participants-as-Treated (APaT) PRO: PRO Full Analysis Set (PRO FAS)
Primary Endpoints/Hypotheses	1) Recurrence-free Survival (RFS) assessed by BICR 2) Overall survival (OS)
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab to placebo on RFS and OS using stratified log-rank tests. Estimation of the hazard ratio (HR) will be performed using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	CCI [redacted]
Multiplicity	

Sample Size and Power	The sample size is approximately 950. CCI [redacted]

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 intervention assignment for this protocol, and the randomization will be implemented in an interactive voice response system.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary

- **Recurrence-free survival (RFS) – assessed by BICR:** RFS: the time from randomization to first documentation of disease recurrence (local, regional, or distant) as assessed by BICR or by pathology consistent with HCC if required per the site's standard of care, or death due to any cause (both cancer and non-cancer causes of death), 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.

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.

9.4.3 PRO Endpoints

The following secondary PRO endpoints will be evaluated as described in Section 4.2.1.3:

- Change from baseline in EORTC QLQ-C30 global health status/quality of life scores, physical functioning score, and role functioning score, as well as abdominal swelling, fatigue, and pain scores from EORTC QLQ-HCC18, and EQ-5D VAS outcome

- Time to confirmed deterioration (TTD) as measured by EORTC QLQ-C30 global health status/quality of life scores, physical functioning score, role functioning score, as well as abdominal swelling, fatigue, and pain scores from EORTC QLQ-HCC18

Based on prior literature [Bjordal, K., et al 2000] [Osoba, D., et al 1998] [King, M. T. 1996], a 10 points or greater worsening from baseline for each scale represents a clinically relevant deterioration for EORTC. TTD is defined as the time from baseline to the first onset of a 10 or more points deterioration from baseline with confirmation at the subsequent visit of a 10 or more points deterioration from baseline.

Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The analyses of efficacy endpoints 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.

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 intervention. Participants will be included in the treatment group corresponding to the study intervention 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 intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives the incorrect study intervention for 1 cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment group and a description 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 intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 PRO Analysis Populations

The PRO analyses are based on the PRO Full Analysis Set (PRO FAS) population, defined as all randomized participants who have at least 1 PRO assessment available for the specific endpoint and have received at least 1 dose of the study intervention. Participants will be analyzed in the treatment group to which they are randomized. PRO FAS populations may be different across EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D.

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. Analysis strategy for key efficacy endpoints is summarized in Table 8. Methods related to exploratory objectives and PRO 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. CCI

9.6.1.1 Recurrence-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the RFS curve in each treatment group. The hypothesis of treatment difference in RFS 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 covariate for treatment will be reported.

Since disease recurrence is assessed periodically, recurrence can occur any time in the time interval between the last assessment where recurrence was not documented and the assessment when recurrence is documented. For the primary analysis, for the participants who have recurrence, the true date of disease recurrence will be approximated by the date of the first imaging assessment at which recurrence is objectively documented and confirmed either radiologically by the BICR vendor or by pathology if required per the site's standard of care, regardless of discontinuation of study intervention. Additional analyses will be performed for comparison of RFS based on investigator's assessment.

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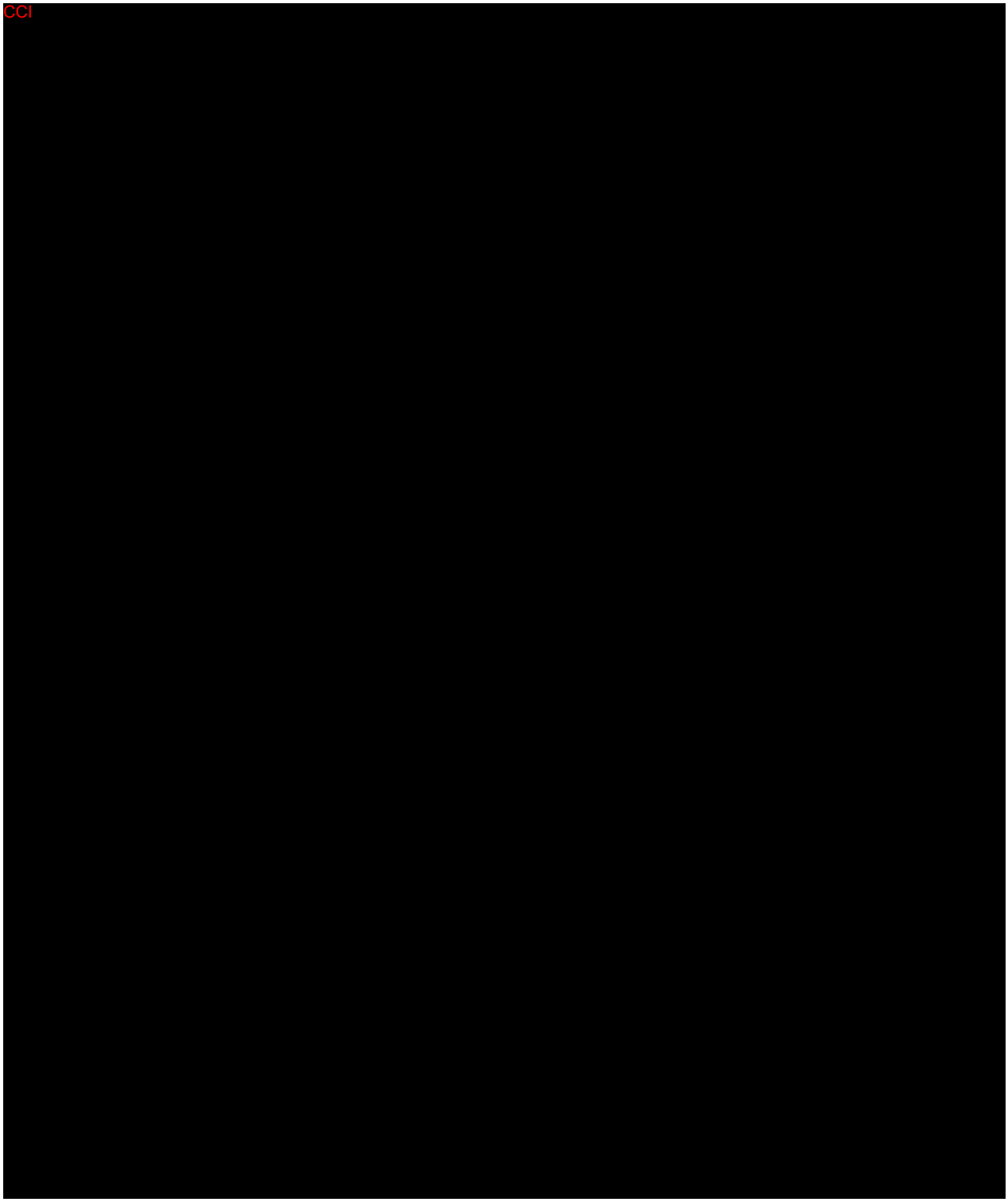


9.6.1.2 Overall Survival

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 covariate for treatment will be reported.

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

Table 8 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Hypothesis (H1)			
RFS by BICR	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis (More details are in Table 7.)
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

BICR=blinded independent central review; ITT=intention-to-treat; OS=overall survival; RFS=recurrence-free survival.
a. Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be applied to the analysis model.

9.6.2 Statistical Methods for Safety Analyses

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

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least 1 AE, a drug-related AE, a serious AE, a serious drug-related AE, a Grade 3-5 AE, a drug-related Grade 3-5 AE, a discontinuation from study intervention due to an AE, and an AE resulting in death. Point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with the event will be provided based on the criteria described below.

Point estimates and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided for AEs that occur in at least 10% of participants in any treatment group. The threshold of at least 10% of participants was chosen because the population enrolled in this study usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, difference in the percentage of participants with specific Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will also be summarized by point estimates and 95% CIs.

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

Table 9 summarizes the analysis strategy for safety endpoints in this study.

Table 9 Analysis Strategy for Safety Parameters

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

9.6.2.2 Assessment of Safety Topics of Special Interest

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

9.6.3 Statistical Methods for Patient-reported Outcome Analyses

The PROs are secondary objectives listed in Section 9.1. No formal hypotheses were formulated. Nominal p-value to compare pembrolizumab arm to the placebo arm may be provided as appropriate. Details of PRO analyses will be described in the sSAP.

9.6.3.1 Change from Baseline

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

To assess the treatment effects on the PRO score change from baseline in the global health status/QoL, physical functioning, role functioning, as well as abdominal swelling, fatigue, and pain scores from EORTC QLQ-HCC18, and EQ-5D VAS outcome, a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger [Liang, K.-Y. and Zeger, S. L. 2000]will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction, and stratification factors used for randomization (see Section 9.5) as covariates.

The treatment difference in terms of least square (LS) mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and postbaseline time point.

9.6.3.2 Time to Confirmed Deterioration (TTD)

The Kaplan-Meier method will be used to estimate the TTD curve for each treatment group. The estimate of median time to deterioration and its 95% CI will be obtained from the Kaplan-Meier estimates. The treatment difference in TTD will be assessed by the stratified log-rank test, and 2-sided nominal p-value will be reported. A stratified Cox proportional hazard model with Efron's method of tie handling and with a single treatment covariate will be used to assess the magnitude of the treatment difference (ie, HR). The HR and its 95% CI will be reported. The same stratification factors used for randomization (see Section 9.5) will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model.

9.6.4 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed using 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 (based on eCRFs), 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. The summary of baseline characteristics will be based on eCRF data.

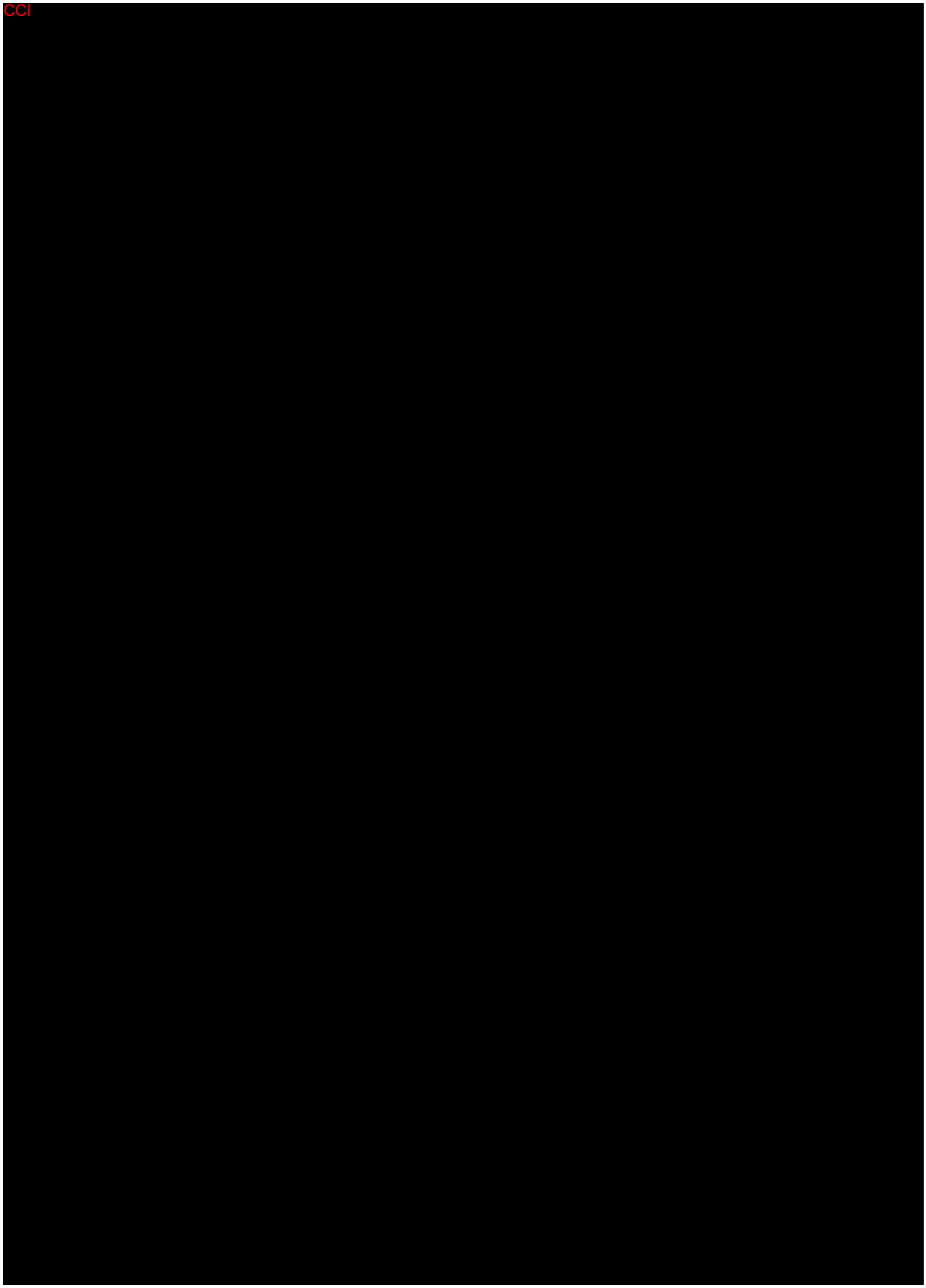
9.7 Interim Analyses

The eDMC will serve as the primary reviewer of the unblinded results of the efficacy and safety analyses and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee (EOC) (see Section 10.1.4.2) of the Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC and limited additional Sponsor personnel may be unblinded to results at the treatment level to act on these recommendations. Additional logistical details will be provided in the eDMC Charter.

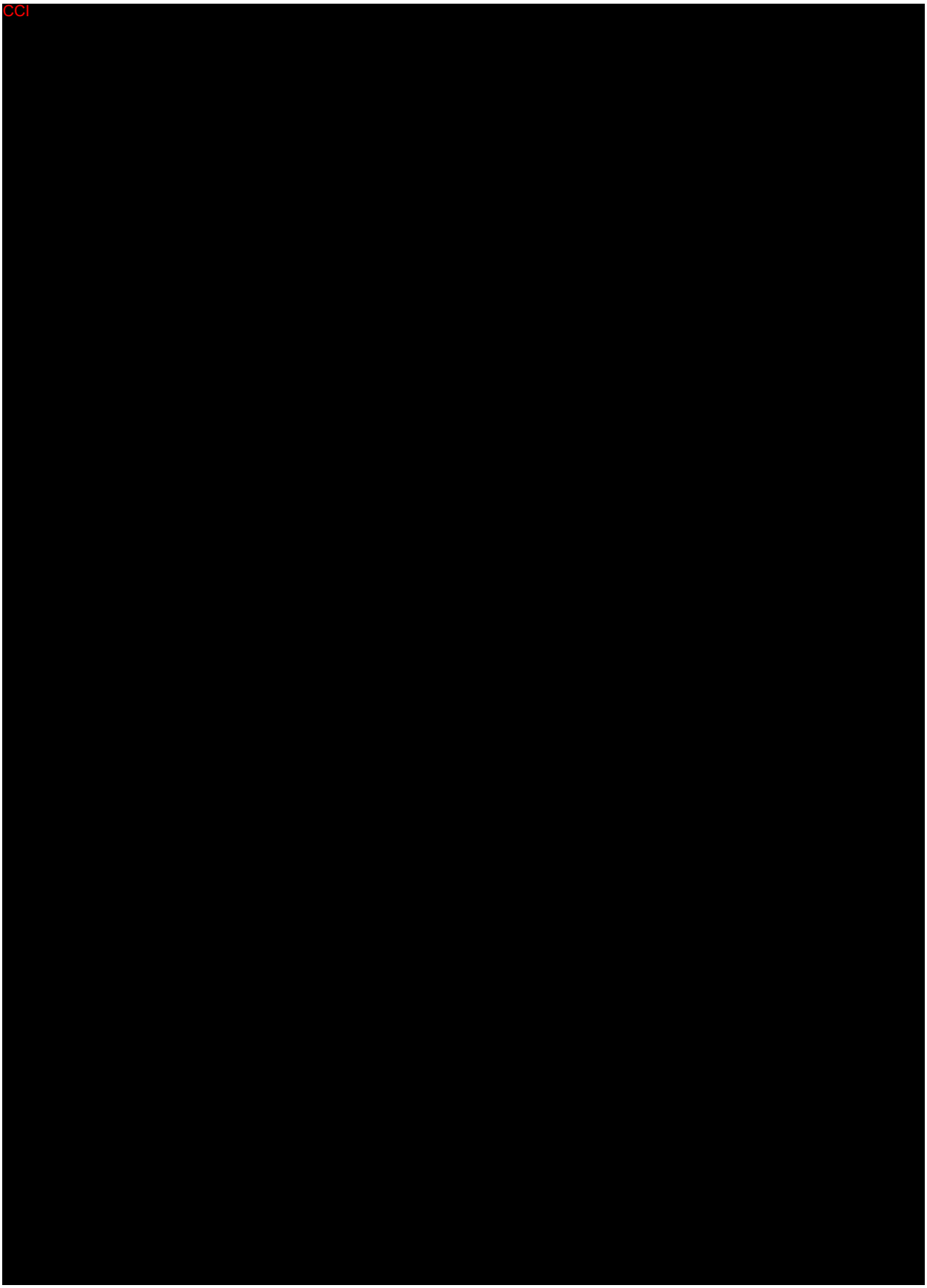
9.7.1 Safety Interim Analyses

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

CCI



CCI



9.8.2 Overall Survival

CCI

[redacted]

9.8.3 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 950 participants in a 1:1 ratio into the pembrolizumab or placebo arms. CCI [redacted]

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

- The control median of 33.8 months for RFS. CCI [redacted]
- CCI [redacted]
- Constant HR for RFS and OS endpoints.
- Enrollment period of 36 months.

- CCI [redacted]

The sample size and power calculations were performed using R ("gsDesign" package).

9.9.2 Sample Size and Power for Safety Analyses

For safety comparisons, risk differences between any 2 treatment groups are summarized in Table 13 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 475 participants for each treatment group.

Table 13 Two-sided 95% CIs of Differences in Incidence of AE Rates Between the Two Treatment Groups for 475 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	(-10.8, -3.6)
11	20.2	-9.2	(-13.8, -4.6)
24.9	36.6	-11.7	(-17.5, -5.9)
43.9	56.5	-12.6	(-18.9, -6.3)
55.7	68	-12.3	(-18.4, -6.2)

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 RFS and OS (with a nominal 95% CI) will be estimated and plotted by treatment group within each category of the following classification variables. All subgroup analyses will be based on the eCRF data.

CCI [redacted]

CCI [redacted]

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. CCI [redacted]

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (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 (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if

potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

All clinical trials will be reviewed and approved by an IRB/IEC and HA 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, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to

enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committee Structure

10.1.4.1 Scientific Advisory Committee

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

10.1.4.2 Executive Oversight Committee

The 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– 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 GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

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

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The tests detailed in Table 14 will be performed by the local laboratory with the exception of hepatitis testing, which will be performed by the central laboratory. Local hepatitis testing is acceptable, including during the screening period, provided LLOD for HBV DNA Viral Load Test is at least 20 IU/mL or less. If hepatitis testing is performed locally, site should report hepatitis tests result in EDC prior to randomization.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Refer to Appendix 7 for country-specific requirements.

Table 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV[a] MCH[a] %Reticulocytes[a]		WBC count with Differential[b]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood Urea Nitrogen (BUN)[c]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Carbon Dioxide (CO_2) or Bicarbonate[a]	Chloride[a]	Phosphorous[a]
	Creatinine[d]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic Pyruvic Transaminase (SGPT)	Total Protein[a]
	Glucose	Calcium	Alkaline phosphatase	Magnesium[a]
	Amylase	Lipase		
Routine Urinalysis	Specific gravity PH, glucose, protein, blood, ketones by dipstick Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Tests	Coagulation panel (PT/INR) Thyroid function tests (T3 [or free T3d], free T4, and TSH) Triglycerides[a] Cholesterol[a] AFP
Other Screening Tests	Follicle stimulating hormone (as needed in women of nonchildbearing potential only) Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP) Serology Anti- HCV, HCV viral load, HCV genotype, anti-HBs, HbsAg, Anti-HBc (total and IgM), HbeAg, HBV viral load, Anti-HDV[e] Serology HIV antibody

AFP=alpha fetoprotein; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CO2=carbon dioxide; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDV=hepatitis D virus (delta agent); INR=International Normalized Ratio; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; WBC=white blood cell; WOCBP=women of child bearing potential.

NOTES:

a. Only required if performed per standard of care.
b. Absolute number or % are acceptable. Absolute number of neutrophils is required.
c. Urea is acceptable if BUN is not available as per institutional standard.
d. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine
e. All study-required laboratory assessments will be performed by a local laboratory, with the exception of hepatitis testing (Anti-HCV, HCV viral load, HCV genotype, anti-HBs, hepatitis B surface antigen [HbsAg], Anti-HBc (total and IgM), HbeAg, HBV viral load, Anti-HDV), which will be performed centrally. Local hepatitis testing is acceptable, including during the screening period, provided LLOD for HBV DNA Viral Load Test is at least 20 IU/mL or less.

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

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are 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.
Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE.

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

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

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

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

Events NOT meeting the AE definition

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

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

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

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

Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

Is a new cancer (that is not a condition of the study)

Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

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

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology 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 self-care ADL.

- Grade 4: Life threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

Assessment of causality

Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

- If no, this is a negative dechallenge.

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

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

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

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

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

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

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

The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

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

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

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

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

Follow-up of AE and SAE

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

New or updated information will be recorded in the CRF.

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

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

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

The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.

Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

Reference Section 8.4.1 for reporting time requirements.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile 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 two FSH measurements in the postmenopausal range is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Female Participants

Contraceptives allowed during the study include[a]:
ghly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
Progestogen-only subdermal contraceptive implant[c] Intrauterine hormone-releasing system (IUS)[d] Non-hormonal 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.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
Progestogen-only hormonal contraception[c] - Oral - Injectable
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. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. d. 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).

10.5.3 Pregnancy Testing

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

After initiation of treatment, additional pregnancy testing will be performed as indicated in Section 1.3 during the treatment period, up to 120 days after the last dose of study intervention or 30 days post dose if new anticancer treatment is started, whichever comes first; or as required locally.

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

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

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. CCI

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, CCI , etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

CCI

CCI

[redacted]

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 China

Section 8.8 Biomarkers

CCI [redacted]
will be collected from participants as specified in the SoA (Note: If a documented law or regulation prohibits [or local IRB/IEC does not approve] sample collection for these purposes, then such samples should not be collected at the corresponding sites):

CCI [redacted]

10.7.2 France

Section 6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

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

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

Please refer to the current pembrolizumab summary of product characteristics for additional guidance on management of immune-related AEs associated with pembrolizumab.

10.7.3 Germany

Section 1.3 Schedule of Activities; Section 8.3.5.2 Pregnancy Test

Monthly urine pregnancy testing is required during study intervention as well as at the end of study intervention.

Section 5.2 Exclusion Criteria

- Exclusion Criterion 8: Hepatitis B and C testing is required for participants.
- Exclusion Criterion 9: HIV testing is required for participants.

Section 6.5.1 Rescue Medications and Supportive Care

- Live vaccines must not be administered for 90 days after the last dose of study intervention.
- Legally Acceptable Representative protocol sections.

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

Section 8.11.1 Screening

Laboratory tests are to be performed within 7 days prior to C1D1. Exceptions are HIV, hepatitis testing, and AFP, which may be conducted up to 28 days prior to the first dose of study intervention.

10.7.4 United Kingdom

Section 6.5 Concomitant Therapy

Live vaccines within 30 days prior to the first dose of study intervention, while receiving study intervention, and for 90 days after the last dose of study intervention, are prohibited. Refer to Section 6.5 for information on COVID-19 vaccines.

10.7.5 Italy

Section 6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

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

- Recurrent Grade 3 colitis

10.7.6 Ireland

Section 1.3 Schedule of Activities

Pregnancy Test – Serum or Urine (WOCBP only): on Day 1 of each cycle, prior to administration of study intervention, and as required by local guidelines up to 120 days after last dose of study intervention or the start of a new anticancer therapy, whichever comes first.

10.7.7 Norway

Section 1.3 Schedule of Activities and Section 8.3.5.2 Pregnancy Test

In Norway, pregnancy testing should be performed monthly for the entire period of contraception requirement (ie, until 120 days post intervention). The use of urine dipsticks at home during the post-treatment period will be allowed unless the results cannot be confirmed as negative (eg, an ambiguous result). In that case, a serum pregnancy test will be required at the clinical site. During the treatment period, pregnancy testing will be performed at the clinical site.

10.7.8 United States (Selected Sites Only)

Section 1.3 Schedule of Activities

Table 15 describes additional administrative and CCI procedures and associated schedule only for participants who elect to participate in the optional CCI at selected sites in the USA. Participation in the CCI at these selected sites is not mandatory for all participants.

Table 15 Study Schedule of Additional Activities for CCI Participants Only

CCI

Section 3 Hypotheses, Objectives, and Endpoints

Objectives	Endpoints
Tertiary/Exploratory	
CCI [redacted]	

CCI [redacted]

CCI

[redacted]

10.7.9 South Korea

Section 1.3 Schedule of Activities and Section 5.1 Inclusion Criteria #9

CCI

[redacted]

10.7.10 Argentina

Section 1.3 Schedule of Activities and Section 8.11.1 Screening

In Argentina, HIV and hepatitis D testing should be performed at screening for all participants, as required by local regulations.

10.7.11 Japan

Section 6.1 Study Intervention(s) Administered

The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in Section 6.1 is based upon guidance issued by the European Commission and applies to countries in the EEA. Diluent placebo (normal saline) for this study is not considered as IMP in Japan.

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

Not applicable.

10.9 Appendix 9: ECOG Performance Status

Developed by the ECOG, Robert L. Comis, MD, Group Chair. [Oken MM, et al 1982]

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

http://ecog-acrin.org/resources/ecog-performance-status

10.10 Appendix 10: Defining Intermediate, High Risk and Very High Risk Patient Populations after Surgical Resection using AJCC 8th Edition Staging

T category	T criteria	Stage	Risk Level
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion	I	
T1a	Solitary tumor ≤2 cm	IA	Intermediate*
T1b	Solitary tumor >2 cm without vascular invasion	IB	Intermediate
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm	II	High
T3	Multiple tumors, at least one of which is >5 cm	IIIA	High
T4*	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein	IIIB	Very High
T4**	Single tumor or multiple with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		

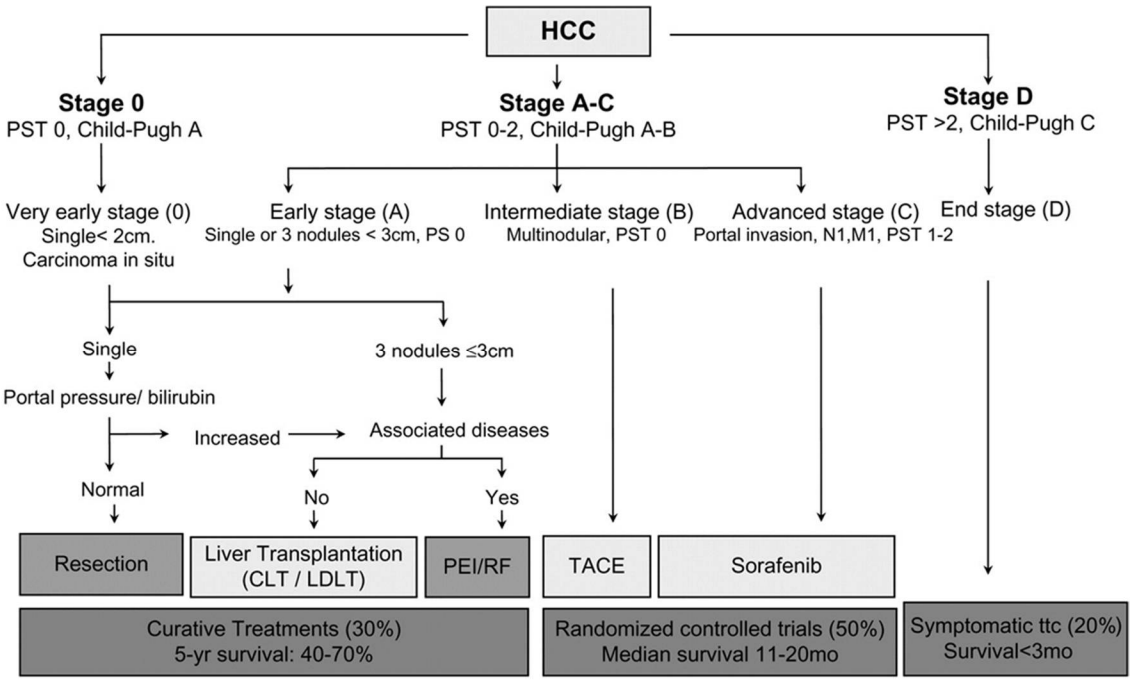
* TIa with solitary tumor = 2 cm may be included as intermediate risk. Any T1a with solitary tumor < 2 cm are not eligible.

**T4 with intrahepatic vascular invasion will be included as very high risk. Any ablation with high-grade pathology may be included for high risk [Kamarajah, S. K., et al 2017].

10.11 Appendix 11: Barcelona Clinic Liver Cancer Staging System

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

Figure 3 Barcelona Clinic Liver Cancer Staging System

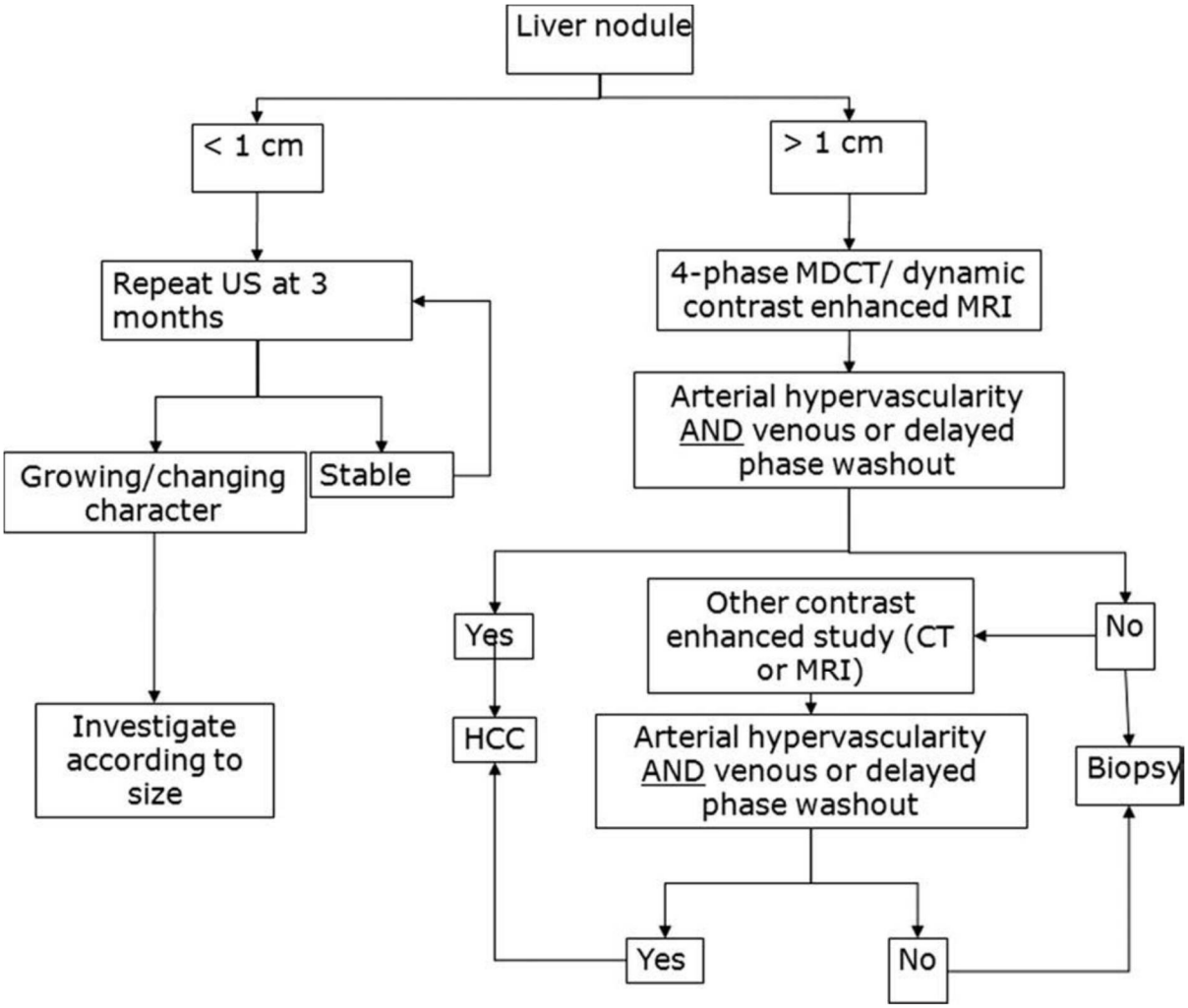


CLT=cadaveric liver transplantation; HCC=hepatocellular carcinoma; LDLT=living donor liver transplantation; PEI=percutaneous ethanol injection; PS=performance status; PST=performance status test; RF=radio frequency (ablation); TACE=transarterial chemoembolization.

10.12 Appendix 12: American Association for the Study of Liver Diseases (AASLD) Criteria

The AASLD diagnostic criteria for suspected HCC are shown in Figure 4 below [Bruix, J. 2011].

Figure 4 Diagnostic Algorithm for Suspected HCC



CT=computed tomography; MDCT=multidetector CT; MRI=magnetic resonance imaging; US=ultrasound.

10.13 Appendix 13: Hepatitis B Definitions and Treatment Considerations

Table 16 describes the various definitions of treatment considerations and eligibility for study participation, along with the definitions of hepatitis B.

Table 16 CCI

CCI

10.14 Appendix 14: 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 a surgical procedure, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation.

Scoring:

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

[1]In primary sclerosing cholangitis and primary biliary cirrhosis, the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/L (4 mg/dL) and the upper limit for 2 points is 170 µmol/L (10 mg/dL).
[2] Different textbooks and publications use different measures. Some older reference works substitute PT prolongation for INR
[3] For patients on anticoagulants (eg, Coumadin), only 1 point is assigned irrespective of the patient's INR and PT value.
[4] Hepatic encephalopathy graded according to West Haven Criteria for Semi-quantitative Grading of Mental Status: *Adapted from: Conn H, Lieberthal M. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins; 1979.*

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

Interpretation:

Chronic liver disease is classified into Child-Pugh class A to C, 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%

10.15 Appendix 15: Abbreviations

Abbreviation	Expanded Term
AASLD	American Association for the Study of Liver Diseases
ADL	activities of daily living
AE	adverse event
AEOSI	adverse event of special interest
AFP	alpha fetoprotein
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
Anti-HCV	hepatitis C antibody
Anti-HDV	hepatitis D antibody
APaT	All Participants as Treated
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BCG	*Bacillus* Calmette–Guérin
BCLC	Barcelona Clinic Liver Cancer
BICR	blinded independent central review(er)
C1D1	Cycle 1 Day 1
CAF	cancer-associated fibroblasts
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRF	Case Report Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DAA	direct acting antivirals
DC	discontinuation
DMC	Data Monitoring Committee
CCI	[redacted]
DNA	deoxyribonucleic acid
EASL	European Association for Study of the Liver
ECG	electrocardiogram
ECI	event(s) of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	External Data Monitoring Committee
EEA	European Economic Area
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	end of treatment

Abbreviation	Expanded Term
EQ-5D-5L	European Quality of Life 5-dimension, 5-level Questionnaire
EuroQoL	European Quality of Life
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HbeAg	hepatitis B early antigen
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV	hepatitis D virus
HECI	hepatic event of clinical interest
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IQR	interquartile range
IRB	Institutional Review Board
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	intervention allocation/randomization system
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LFT	liver function test
LLOD	lower limit of detection
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NDA	New Drug Application

Abbreviation	Expanded Term
NIMP	non-investigational medicinal product
NSCLC	non-small cell lung cancer
NT	not transplantable
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PBPK	physiologically based PK
PDLC	predefined limits of change
PFS	progression-free survival
PK	pharmacokinetic
PRO	patient-reported outcomes
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QoL	quality of life
RBC	red blood cells
RCC	renal cell carcinoma
RFS	recurrence-free survival
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SBRT	stereotactic body radiation therapy
SIM	Site Imaging Manual
SoA	schedule of activities
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TIL	tumor-infiltrating lymphocytes
TMDD	target-mediated drug disposition
TME	tumor microenvironment
CCI	[redacted]
TSH	thyroid-stimulating hormone
CCI	[redacted]
ULN	upper limit of normal
USA	United States of America
VAS	visual analog scale
WOCBP	woman/women of childbearing potential

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