Official Protocol Title:	A Phase 3 Randomized, Double Blind Study of Pembrolizumab Plus Gemcitabine/Cisplatin versus Placebo Plus Gemcitabine/Cisplatin as First-Line Therapy in Participants with Advanced and/or Unresectable Biliary Tract Carcinoma
NCT number:	NCT04924062
Document Date:	16-June-2022

Title Page

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

Protocol Title: A Phase 3 Randomized, Double Blind Study of Pembrolizumab Plus Gemcitabine/Cisplatin versus Placebo Plus Gemcitabine/Cisplatin as First-Line Therapy in Participants with Advanced and/or Unresectable Biliary Tract Carcinoma

Protocol Number: 966-06

Compound Number: MK-3475

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as 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	123482
EudraCT	2019-000944-82

Approval Date: 16 June 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 6	16-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 5	18-NOV-2021	To add a new, earlier interim analysis for OS due to recently emerging external data showing positive results for immunotherapy plus chemotherapy as first-line therapy for patients with advanced biliary tract carcinoma, and CCI [redacted] CCI [redacted]
Amendment 4	26-AUG-2021	To update Statistical Analysis plan accounting for faster event accumulation than initially projected by increasing the number of events at final analysis and specifying time and event triggers for analyses to ensure sufficient minimum follow-up time for a longer potential delayed effect.
Amendment 3	11-MAR-2021	The Dose Modification and Toxicity Management Guidelines for irAEs and table were updated to align with the USPI CCI [redacted] In addition, CCI [redacted] updates were made to address CCI [redacted] Cisplatin unit dose strengths were added.
Amendment 2	08-DEC-2020	To revise the primary endpoint to OS only with a more conservative hazard ratio assumption accounting for possible delayed treatment effect; to change PFS to a secondary endpoint; and to remove the futility analysis. Also, to update interim and final analysis timing from calendar-based to event based.

Document	Date of Issue	Overall Rationale
Amendment 1	23-JAN-2020	To limit the second course only to those participants who received pembrolizumab in the first course after unblinding participants individually, to address CCI [redacted] CCI and minimize unnecessary participant visits and procedures.
Original Protocol	21-JUN-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendments:

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.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Double Blind Study of Pembrolizumab Plus Gemcitabine/Cisplatin versus Placebo Plus Gemcitabine/Cisplatin as First-Line Therapy in Participants with Advanced and/or Unresectable Biliary Tract Carcinoma

Short Title: Pembrolizumab or Placebo Plus Gemcitabine/Cisplatin for First-Line Advanced and/or Unresectable BTC

Acronym: KEYNOTE-966

Hypotheses, Objectives, and Endpoints:

In first-line therapy for participants with advanced and/or unresectable biliary tract carcinoma:

Although the original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, throughout this protocol, the term RECIST 1.1 refers to an adjustment of RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. Refer to Section 4.2.2.2 for further details.

Primary Objectives	Primary Endpoints
- Objective: To compare overall survival (OS) between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin - Hypothesis (H1): Pembrolizumab plus gemcitabine/cisplatin is superior to placebo plus gemcitabine/cisplatin with respect to OS	- OS: the time from randomization to death due to any cause
Secondary Objectives	Secondary Endpoints
- Objective: To compare progression-free survival (PFS) per RECIST 1.1 as assessed by blinded independent central review (BICR) between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin - Hypothesis (H2): Pembrolizumab plus gemcitabine/cisplatin is superior to placebo plus gemcitabine/cisplatin with respect to PFS per RECIST 1.1 by BICR	- PFS: the time from randomization to the first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first

- Objective: To compare objective response rate (ORR) per RECIST 1.1 as assessed by BICR between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin - Hypothesis (H3): Pembrolizumab plus gemcitabine/cisplatin is superior to placebo plus gemcitabine/cisplatin with respect to ORR per RECIST 1.1 as assessed by BICR	- Objective Response (OR): complete response (CR) or partial response (PR)
- Objective: To evaluate duration of response (DOR) per RECIST 1.1 as assessed by BICR	- DOR: for participants who demonstrate confirmed CR or PR, the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first
- Objective: To evaluate the safety and tolerability profile of pembrolizumab plus gemcitabine/cisplatin	- Adverse events (AEs) - Study intervention discontinuations due to AEs

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Biliary Tract Carcinoma
Population	Participants with Advanced and/or Unresectable Biliary Tract Carcinoma (Intrahepatic, Extrahepatic, or Gallbladder)
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	Sponsor Investigator Participant

Estimated Duration of Study	The Sponsor estimates that the study will require approximately 38 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. **Extension Portion of the Study in China:** The study may remain open longer than 38 months to complete a potential extension portion of the study in China.

Number of Participants:

Approximately 1048 participants will be randomized 1:1 with approximately 524 participants in each arm to the global portion of this study. After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until approximately 158 participants from China have been enrolled to meet local regulatory requirements.

Intervention Groups and Duration:

Intervention Groups

Inter-vention Group Name	Drug	Dose Strength	Dose Frequency	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A	Pembrolizumab	200 mg	Q3W	IV Infusion	Day 1 of each cycle for up to 35 administrations	Experimental
	Gemcitabine	1000 mg/m^2	Q3W	IV Infusion	Day 1 and Day 8 of each cycle until PD or unacceptable toxicity	Background Treatment
	Cisplatin	25 mg/m^2	Q3W	IV Infusion	Day 1 and Day 8 of each cycle for up to 8 cycles	Background Treatment
Arm B	Placebo	N/A	Q3W	IV Infusion	Day 1 of each cycle for up to 35 administrations	Experimental
	Gemcitabine	1000 mg/m^2	Q3W	IV Infusion	Day 1 and Day 8 of each cycle until PD or unacceptable toxicity	Background Treatment
	Cisplatin	25 mg/m^2	Q3W	IV Infusion	Day 1 and Day 8 of each cycle for up to 8 cycles	Background Treatment

Abbreviations: IV=intravenous, PD=disease progression, Q3W=every 3 weeks

Other current or former name(s) or alias(es) for study intervention(s) are as follows: Pembrolizumab, MK-3475

Total Number of Intervention Groups/ Arms	2 arms
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants who complete study intervention after receiving 35 administrations of pembrolizumab and without disease progression or intolerability, or participants who attain a complete response and stop study intervention with pembrolizumab may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy. Participants who discontinue study intervention for reasons other than radiographic disease progression will have post-intervention follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study. Once the study has ended, the participant is discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

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.	

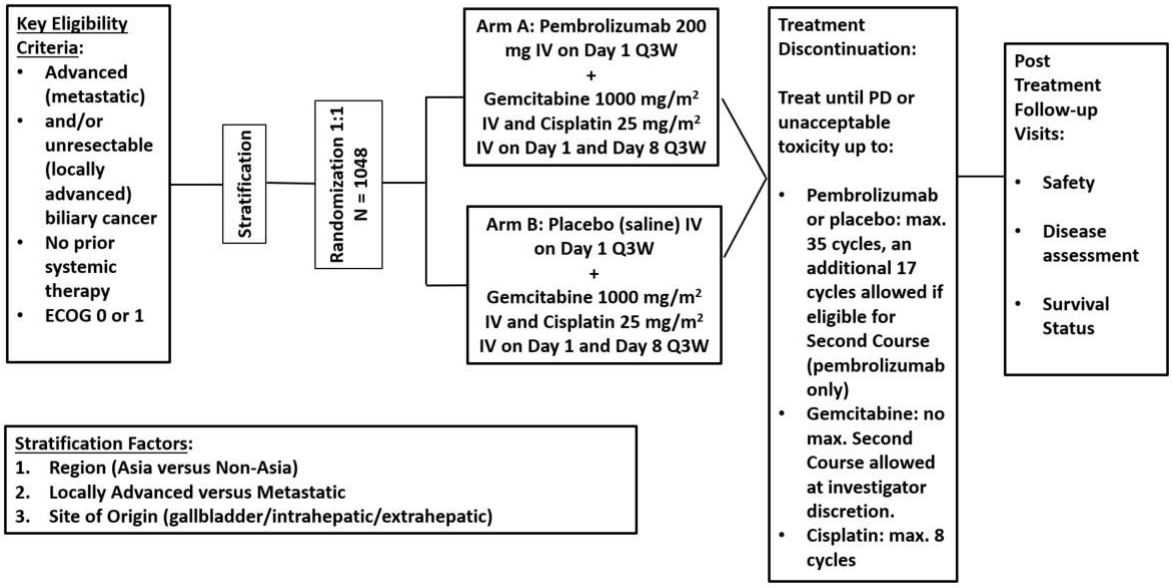
Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



Abbreviations: ECOG=Eastern Cooperative Oncology Group; IV=intravenous; max = maximum; PD=progressive disease; Q3W=every 3 weeks

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities Initial Intervention Phase

Table 1 Study Schedule of Activities – Initial Intervention

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Administrative and General Procedures												
Informed Consent	X											Documented informed consent can be obtained at any time before any protocol-specific screening procedures being performed. If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.
Informed Consent for Future Biomedical Research	X											Participation in FBR is optional, but documented informed consent is mandatory if participating and should be performed before obtaining samples for FBR (refer to Section 8.9).
Inclusion/ Exclusion Criteria	X											

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Participant ID Card	X	X										Update ID card at randomization visit with randomization number.
Demographics	X											
Medical/Surgical Histories (including investigator-assessed risk factor for biliary cancer, smoking and alcohol use)	X											Smoking and alcohol use will be collected on eCRF. Investigators will be asked to enter biliary cancer risk factors (gallstones, infections, autoimmune diseases, cirrhosis, primary sclerosing cholangitis, and others/unknown).
Prior and Concomitant Medication Review	X	X	X	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. Note: All corticosteroid use must be reported. CM review on Day 8 is not required after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Randomization and Study Treatment Assignment via IRT		X										Randomization must be completed within 3 days before C1D1 and after confirmation of eligibility. All procedures and assessments on C1D1 should be performed after randomization.
Subsequent Antineoplastic Treatment Status									X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinic visit is not feasible, follow-up information may be obtained via other means of contact (eg, telephone, video call, mail or email).
Survival (Vital) Status		←----------									----------→	Upon Sponsor request, participants may be contacted for survival (vital) status at any time during the course of the study.
Administration of Study Intervention												
Pembrolizumab or Placebo		X		X		X						Pembrolizumab 200 mg IV Q3W or placebo (normal saline) IV Q3W for up to 35 administrations. Refer to Section 8.1.8.1. for timing and order of dose administration.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Gemcitabine		X	X	X	X	X	X					1000 mg/m^2 IV on Day 1 and Day 8 Q3W until PD or unacceptable toxicity. Refer to Section 8.1.8.1. for timing and order of dose administration.
Cisplatin		X	X	X	X	X (Up to Cycle 8)	X (Up to Cycle 8)					25 mg/m^2 IV on Day 1 and Day 8 Q3W for up to 8 cycles. Refer to Section 8.1.8.1. for timing and order of dose administration.
Efficacy Procedures												
Tumor Imaging – (CT of the chest, CT or MRI of the abdomen and pelvis)	X	<---------->						X		X		On study imaging assessment must be performed 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) through Week 54. Participants who remain on treatment beyond Week 54 will have imaging performed every 12 weeks (84 days ±7 days). All imaging assessments should follow calendar days and not be adjusted for cycle delays. Imaging at EOI is not required if the previous tumor imaging assessment was within 4 weeks before the EOI visit. Refer to Section 8.2.1 for additional details for tumor imaging assessment.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Clinical Procedures or Assessments												
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X		AEs: monitored up to 30 days after last dose. SAEs: monitored up to 90 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever occurs first. AE review on Day 8 is not required after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.
Full Physical Examination	X							X				Perform within 14 days before the start of study intervention.
Directed Physical Examination		X	X	X	X	X	X		X			Conduct on Day 1 and Day 8 of each cycle before administration of study intervention. Conducting within 1 day before administration of study intervention is acceptable. Note: Day 8 directed physical examination is not required after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Audiometry	X											Perform at Screening, or as required per local standard, repeat if clinically indicated.
Vital Signs and Weight	X	X	X	X	X	X	X	X	X			Refer to Section 8.3.3, vital signs include blood pressure, pulse rate, respiratory rate, and temperature. Conducting within 1 day before administration of study intervention is acceptable. Note: Day 8 vital signs and weight are not required after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.
Height	X											
12-lead ECG	X											Perform single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes before the ECG.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
ECOG Performance Status	X	X	X	X	X	X	X	X	X			If ECOG is performed before dosing on C1D1, then Screening ECOG is not mandatory. Should be assessed before dosing at treatment visits. Conducting within 1 day before administration of study intervention is acceptable. Note: Day 8 ECOG PS will not be performed after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Local Laboratory Procedures and Assessments[c]												
Pregnancy Test (WOCBP only)[d]	X	X		X		X		X	X			Assess within 24 hours (urine) or 72 hours (serum) before study intervention administration on Day 1 of each cycle. If pregnancy testing during the Screening Phase occurs within 24 hours (urine) or 72 hours (serum) before the first dose, it does not have to be repeated at C1D1. In regions where required via documented regulatory request (and subsequently approved by the Sponsor), pregnancy tests within 24 hours prior to treatment allocation will be required. During the Post-Intervention Phase, perform a serum or urine pregnancy test approximately 240 days after the last dose of chemotherapy or 150 days after the last dose of pembrolizumab or placebo, whichever is greater, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy. Pregnancy testing should be conducted as per local regulations, where applicable.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
PT/INR and aPTT	X											Screening: collect within 14 days before the first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy. Refer to Section 6.5 for additional requirements during gemcitabine administration.
Hematology	X	X	X	X	X	X	X	X	X			Screening: perform within 14 days before the first dose of study intervention. Perform on Day 1 and Day 8 before administration of study intervention (within 1 day before administration of study intervention is acceptable). For laboratory details refer to Section 10.2, Appendix 2, Table 18. Note: Day 8 hematology blood samples will not be collected after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Chemistry Panel and Liver Panel	X	X	X	X	X	X	X	X	X			Screening: perform within 14 days before the first dose of study intervention. Collect liver panel on Day 1 and Day 8 before administration of study intervention (within 1 day before administration of study intervention is acceptable). For laboratory details refer to Section 10.2, Appendix 2, Table 18. Note: Day 8 chemistry and liver panel blood samples will not be collected after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.
Urinalysis	X								X			Screening: perform within 14 days before the first dose of study intervention. Repeat as clinically indicated.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
T3, FT4, and TSH	X			X		X (Even Cycles)		X				Screening: perform within 14 days before the first dose of study intervention. If testing is performed centrally, must perform within 28 days. Perform on Day 1 of every other cycle starting from Cycle 2 (eg, Cycle 2, 4, 6, 8, etc) and at EOI. After Cycle 1, participant may be dosed even if thyroid evaluations are not available prior to dosing; however, the results must be available and reviewed before the next scheduled visit. Free T3 is acceptable where T3 cannot be determined.
Tuberculosis screening[d]	X											Per local regulations.
HIV[d]	X											Per local regulations.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Central Laboratory Assessments[c]												
Anti-HCV (IgG)	X											
<u>If Anti-HCV (IgG) positive:</u>												If these conditions are met, the following test will be performed within 28 days before study intervention. For repeat hepatitis 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 the Sponsor.
HCV viral load	X											Participants with no HBV infection may be randomized if HCV viral load samples were drawn before randomization and results are pending at the time of randomization. For repeat hepatitis 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 the Sponsor.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Anti-HBc (total and IgM), HBV viral load, HBsAg	X											For participants not taking HBV antiviral therapy, repeat HBV viral load and HBsAg tests approximately every 6 weeks if HBsAg negative, anti-HBc positive, and HBV viral load is undetectable at screening. Repeat HBV viral load and HBsAg tests approximately every 12 weeks for all participants on HBV antiviral therapy until the end of study intervention and then per local standard of care. This testing should be aligned with study intervention visits. For HBV viral load over 100 IU/mL start HBV treatment. For repeat hepatitis 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 the Sponsor.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
PK/Pharmacodynamic/Biomarker Assessment												
Pembrolizumab Pharmacokinetics		X		X		X (C4, and every 4 cycles starting there-after)						Predose PK and ADA samples will be collected at Day 1 of Cycles 1, 2, 4 and every 4 cycles thereafter (eg, C8, C12, C16, etc). All predose samples should be drawn within 24 hours before infusion of pembrolizumab or placebo. Additional postdose peak PK samples will be drawn within 30 mins (+15 minutes time window) after the end of pembrolizumab or placebo infusion at Cycle 1 and Cycle 8.
Pembrolizumab Antidrug Antibodies		X		X		X (C4, and every 4 cycles there-after)						Predose PK and ADA samples will be collected at Day 1 of Cycles 1, 2, 4 and every 4 cycles thereafter (eg, C8, C12, C16, etc). All predose samples should be drawn within 24 hours before infusion of pembrolizumab or placebo.
CCI [redacted]		X										If sample is not available at C1D1, it may be collected at a subsequent visit.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
CCI Analysis[d,e]		X										Collect predose C1D1. This sample should be drawn for planned analysis of CCI CCI Refer to Section 8.8.1 for additional details.
CCI CCI Analysis[d]		X		X		X (C5)		X				Collect predose.
CCI CCI Analysis[d]		X		X		X (C5)		X				Collect predose.
CCI Analysis[d]		X		X		X (C5)		X				Collect predose.
CCI Analysis[d]		X		X		X (C5)		X				Collect predose.
CCI analysis (optional)[d]		X		X		X (C5)		X				Collection at home within 1 week before the specified visit and brought into site on C1D1, C2D1, C5D1, and at EOI.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	
Archival or Newly Obtained Tissue Collection[d]	X											Tissue is required for enrollment. The tumor tissue must be received by the central vendor and deemed adequate for CCI [redacted]. Refer to Section 8.8.2 for additional information.
Patient-reported Outcomes												
ePROs in the following order: EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BIL21		X		X		X		X	X			Administer questionnaires before the AE evaluation, disease status notification, and dosing on Day 1 of Cycle 1 through Cycle 10 and every 2 cycles thereafter (ie, Cycles 12, 14, 16, 18) up to Cycle 18, at EOI, and at the 30-day Safety Follow-up.

Study Period	**Screening Phase[a]**	**Study Intervention Phase 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle(s)		**Cycle 1**		**Cycle 2**		**Cycles 3 to last Cycle**			**Safety FU[b]**	**(Efficacy) FU**	**Survival FU**	
Day		**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**–28 to –1**		**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (± 7 days)**	**Q12W (± 7 days)**	

Abbreviations: ADA=antidrug antibodies; AE=adverse event; Anti-HBc=hepatitis B core antibody; Anti-HCV=hepatitis C virus antibody; aPTT=activated partial thromboplastin time; C1D1=Cycle 1 Day 1; CM=concomitant medication; CT=computed tomography; ctDNA=circulating tumor DNA; CX=Cycle X; D/C=discontinuation; DNA=deoxyribonucleic acid; DX=Day X; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOI=end of intervention; EORTC=European Organisation for Research and Treatment of Cancer; ePRO=electronic patient-reported outcome; FBR=future biomedical research; FT4=free thyroxine; FU=follow-up; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ID=identification; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; IRT=interactive response technology; IV=intravenous; MRI=magnetic resonance imaging; MSI=microsatellite instability; PCR=polymerase chain reaction; PD=disease progression; PD-L1= programmed cell death ligand 1; PK=pharmacokinetics; PS=performance status; PT=prothrombin time; Q3W=every 3 weeks; Q6W=every 6 weeks; Q12W=every 12 weeks; QLQ=Quality of Life Questionnaire; RNA=ribonucleic acid; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

a. Screening procedures can be performed within 28 days before randomization, unless otherwise specified.
b. If EOI visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOI visit and the Safety Follow-up Visit should be performed.
c. Clinical laboratory assessments may be conducted any time within 72 hours before the scheduled visit, unless otherwise specified. Procedures/assessments should be performed before administration of study intervention.
d. Refer to Section 10.7 (Appendix 7) for country-specific requirements.

CCI

[redacted]

1.3.2 Schedule of Activities Second Course Phase

Table 2 Schedule of Activities – Second Course Phase (Retreatment)

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
Administrative and General Procedures											
Eligibility Criteria	X										
Concomitant Medication Review	X	X	X	X	X	X	X	X			Enter new medications started during the study through the post-treatment Safety Follow-up. Record concomitant medications beyond 30 days after treatment discontinuation if related to SAE or ECI. CM review on Day 8 is not required after gemcitabine is permanently discontinued.
Subsequent Antineoplastic Treatment Status								X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinic visit is not feasible, follow-up information may be obtained via other means of contact (eg, telephone, video call, mail, or email).
Survival (Vital) Status	<---------->									X	Upon Sponsor request, participants may be contacted for survival (vital) status at any time during the course of the study.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
Administration of Study Intervention											
Pembrolizumab	X		X		X						Pembrolizumab 200 mg IV Q3W for up to 17 administrations. Refer to Section 8.1.8.1. for timing and order of dose administration.
Gemcitabine	X	X	X	X	X	X					The decision of whether or not to continue gemcitabine during second course will be at the discretion of the investigator. If continued, the dose of gemcitabine will be given in clinic on Day 1 and Day 8 of each SC cycle. Refer to Section 8.1.8.1. for timing and order of dose administration. Treatment with gemcitabine will continue until unacceptable toxicity or PD.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
Efficacy Procedures											
Tumor Imaging - (CT of the chest, CT or MRI of the abdomen and pelvis)[b]	<---------->						X		X		Tumor imaging should be performed within 28 days before restarting study intervention. The initial second course imaging assessment should be performed at 6 weeks (42 days +7 days) after the restart of study intervention. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated. All imaging assessments should follow calendar days and not be adjusted for cycle delays. Imaging at EOI is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOI visit. Refer to Section 8.2.1 for additional details on tumor imaging assessment.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
Clinical Procedures or Assessments[b]											
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X		AEs: monitored up to 30 days after last dose. SAEs: monitored up to 90 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever occurs first. AE review on Day 8 is not required after gemcitabine is permanently discontinued.
Vital Signs and Weight	X	X	X	X	X	X	X	X			Refer to Section 8.3.3, vital signs include blood pressure, pulse rate, respiratory rate, and temperature. Conducting within 1 day before administration of study intervention is acceptable. Note: Day 8 vital signs and weight will not be performed after gemcitabine is permanently discontinued.
Full Physical Examination	X						X				Perform within 14 days prior to start of study intervention for second course.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
Directed Physical Examination		X	X	X	X	X		X			Conduct on Day 1 and Day 8 of each cycle prior to the administration of study intervention. Conducting within 1 day before administration of study intervention is acceptable. Note: Day 8 directed physical examination is not required after gemcitabine is permanently discontinued.
ECOG Performance Status	X	X	X	X	X	X	X	X			Should be assessed prior to dosing at treatment visits. Conducting within 1 day before administration of study intervention is acceptable. Note: Day 8 ECOG PS will not be performed after gemcitabine is permanently discontinued.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
Local Laboratory Procedures and Assessments[b]											
Pregnancy Test (WOCBP only)[c]	X		X		X		X	X			Assess within 24 hours (urine) or 72 hours (serum) prior to study intervention administration on Day 1 of each cycle. In regions where required via documented regulatory request (and subsequently approved by the Sponsor), pregnancy tests within 24 hours prior to study intervention will be required. During the Post-Intervention Phase, perform a serum or urine pregnancy test at least 240 days after the last dose of chemotherapy or 150 days after the last dose of pembrolizumab, whichever is greater, or 30 days after cessation of study intervention if the participant initiates a new anticancer therapy. Pregnancy testing should be conducted as per local regulations where applicable.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
PT/INR and aPTT	X										Collect samples within 14 days before starting second course study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy. Refer to Section 6.5 for additional requirements during gemcitabine administration.
Hematology	X	X	X	X	X	X	X	X			Perform within 14 days before starting second course study intervention. Perform on Day 1 and Day 8 before administration of study intervention (within 1 day before administration of study intervention is acceptable). For laboratory details refer to Section 10.2, Appendix 2, Table 18. Note: Day 8 hematology blood samples will not be performed after chemotherapy is permanently discontinued.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
Chemistry Panel and Liver Panel	X	X	X	X	X	X	X	X			Perform within 14 days before starting second course study intervention. Collect liver panel on Day 1 and Day 8 before administration of study intervention (within 1 day before administration of study intervention is acceptable). For laboratory details refer to Section 10.2, Appendix 2, Table 18. Note: Day 8 chemistry and liver panel blood samples will not be performed after gemcitabine is permanently discontinued.
Urinalysis	X							X			Perform within 14 days prior to starting second course study intervention.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
T3, FT4, and TSH	X		X		X (Even Cycles)		X				Perform within 14 days prior to starting second course study intervention. Perform on Day 1 of every other cycle starting from Cycle 2 (eg, Cycle 2, 4, 6, 8, etc) and at EOI. After Cycle 1, participant will be dosed even if thyroid evaluations are not available prior to dosing; however, the results must be available and reviewed before the next scheduled visit. Free T3 is acceptable where T3 cannot be determined.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**						**EOI**	**Post-Intervention**			**Notes**
Intervention Cycle	**Cycle 1**		**Cycle 2**		**Cycles 3 to17**			**Safety FU[a]**	**Efficacy FU**	**Survival FU**	
Day	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**					
Scheduling Window (Days):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At Time of D/C**	**30 Days After Last Dose (+ 7 days)**	**Q6W or Q12W (±7 days)**	**Q12W (± 7 days)**	
Central Laboratory Assessments[b]											
HBsAg and HBV viral load	X										For participants not taking HBV antiviral therapy, repeat HBV viral load and HBsAg tests approximately every 6 weeks if HBsAg negative and anti-HBc positive, and HBV viral load is undetectable at screening. Repeat HBV viral load and HBsAg tests approximately every 12 weeks for all participants on HBV antiviral therapy until the end of study intervention and then per local standard of care. This testing should be aligned with study intervention visits. For HBV viral load over 100 IU/mL, start HBV treatment.

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CT=computed tomography; D/C=discontinuation; DX=Day X; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EOI=End of intervention; FT4=free thyroxine; FU=Follow-up; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; INR=international normalized ratio; IV=intravenous; MRI=magnetic resonance imaging; PD=disease progression; PS=performance status; PT=prothrombin time; Q3W=every 3 weeks; Q6W=every 6 weeks; Q12W=every 12 weeks; SAE=serious adverse event; SC=second course; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

a. If EOI visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. In this situation, all procedures required at both the EOI visit and the Safety Follow-up Visit should be performed.
b. Clinical laboratory assessments may be conducted anytime within 72 hours before the scheduled visit, unless otherwise specified. Procedures/assessments should be performed before administration of study intervention.
c. Refer to Section 10.7 (Appendix 7) for country-specific requirements.

2 INTRODUCTION

2.1 Study Rationale

Biliary tract cancer (BTC) comprises cancers of intra- and extrahepatic bile ducts (cholangiocarcinoma [CCA]) and gallbladder. Biliary tract cancer is a rare but aggressive malignancy with limited treatment options. The majority of patients present with advanced or unresectable disease and undergo systemic chemotherapy. Patients presenting with earlier stage disease may undergo curative surgical resection but have a high rate of recurrence and metastases [Zhu, A. X., et al 2010] [Margonis, G. A., et al 2016]. Gemcitabine in combination with cisplatin is the standard of care (SOC) first-line therapy worldwide, with S-1 (an oral fluoropyrimidine containing tegafur, gimeracil, and oteracil) also being used in Japan. Despite advances in supportive care along with combination chemotherapy, median PFS is approximately 6 to 7 months, and the median survival of advanced BTC patients remains dismal at approximately 12 months [Valle, J., et al 2010] [Okusaka, T., et al 2010]. An additional challenge in this patient population is the high risk of infection due to frequent biliary obstruction, particularly when exposed to immunosuppressive combination chemotherapy regimens. Poor prognosis and limited treatment options in this challenging cancer highlight the unmet medical need for more effective therapies for those with advanced disease.

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 a number of 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 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. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an 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. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010].

2.2.2 Biliary Tract Cancer: Epidemiology and Current Therapeutic Options

Biliary tract cancer arises from the epithelial lining of the biliary tree and is comprised of cancers of the bile ducts called cholangiocarcinoma (CCA), gallbladder, and ampulla. Cholangiocarcinoma is classified as intrahepatic or extrahepatic. Ampullary cancers have been excluded from the current protocol due to potentially better prognosis [Hatzaras, I., et al 2010] [Park, I., et al 2009]. Additionally, ampullary cancer diagnosis and distinction from pancreatic and duodenal cancers could be challenging in a global study. Biliary tract cancer subtypes differ in their cancer biology, clinical presentation, and are often diagnosed in the advanced stage. Nonetheless, for advanced or metastatic BTC (CCA and gallbladder), platinum-based chemotherapy is the SOC irrespective of subtype.

BTC also has a variable geographic distribution and incidence. Based on Surveillance, Epidemiology, and End Results Program (SEER) data the estimated incidence of BTCs in United States in 2018 was about 17,000 cases per year (including biliary, which account for approximately10 % of liver and bile duct cancers) [Siegel, R. L., et al 2018]. In the West, the incidence of CCA is low, while in Asia (eg, Thailand, China, Korea, Vietnam), rates are much higher [Bragazzi, M. C., et al 2012]. Northeast Thailand has the highest CCA rate in the world, accounting for >80% of all primary liver cancers [Shin, H. R., et al 2010]. Similarly, the incidence of gallbladder cancer (GBC) in the West is generally low; however, it is a significant health problem in Chile, India and Central/Eastern Europe. There are various risk factors associated with BTC. High rates of liver fluke infection have been associated with CCA risk in Asia. Gallstones and *Salmonella* Typhi infections are considered

to be strong risk factors for GBC in India and Chile [Lazcano-Ponce, E. C., et al 2001]. In Europe and the United States, inflammatory disorder of the biliary tract, primary sclerosing cholangitis, and fibro-polycystic liver disease have been associated with BTC. Other general risk factors include intrahepatic stone disease, chronic liver disease, biliary papillomatosis, and genetic predisposition in Lynch syndrome.

Systemic combination chemotherapy consisting of gemcitabine and cisplatin is the SOC first-line therapy in most countries for patients with advanced BTC. This is based on the study ABC-02 [Valle, J., et al 2010]. ABC-02 was a randomized Phase 3 study with a primary end of OS and enrolled 410 participants. Cisplatin 25 mg/m^2 followed by gemcitabine 1000 mg/m^2, each administered on Days 1 and 8, Q3W for 8 cycles, was shown to be associated with improved OS compared to single agent gemcitabine (1000 mg/m^2 on Days 1, 8, and 15, every 4 weeks for 6 cycles) (11.7 months versus 8.1 months respectively; hazard ratio [HR] 0.64, 95% CI: 0.52–0.80, p <0.001). In ABC-02, dose modifications and delays were allowed for hematologic toxicity, abnormal renal function, nausea, vomiting, peripheral neuropathy, edema, or tinnitus. There was one death from renal failure in the gemcitabine and cisplatin group, possibly related to cisplatin.

A similar randomized Phase 2 study (BT22) with cisplatin 25 mg/m^2 followed by gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle or single agent gemcitabine 1000 mg/m^2 on Days 1, 8 and 15 of a 28-day cycle was conducted in Japan and showed an improvement in one-year survival rate (11.2 months versus 7.7 months; HR 0.69, 95% CI: 0.42-1.13, p <0.139), median PFS (5.8 months versus 3.7 months; HR 0.66, 95% CI: 0.41-1.05, p <0.077) and ORR (19.5% versus 11.9%) favoring the combination of gemcitabine and cisplatin compared to single agent gemcitabine [Okusaka, T., et al 2010]. In BT22, the most common AEs were related to myelosuppression seen in both groups but more common with combination therapy, as anticipated. Overall, the gemcitabine and cisplatin combination was well tolerated in both ABC-02 and BT22.

In Japan, an alternative first-line option is gemcitabine in combination with S-1. This is based on a Phase 3 study (FUGA-BT; JCOG1113) that demonstrated noninferiority of gemcitabine plus S-1 when compared to gemcitabine plus cisplatin [Mizusawa, J., et al 2016]. However, S-1 is not currently approved in multiple countries, hence, there is limited access to this regimen. Other potential options include 5- fluorouracil based options, gemcitabine with oxaliplatin (GEMOX), and taxane (docetaxel and paclitaxel) combinations. GEMOX was studied both in first-line and refractory settings in a Phase 2 study. An ORR of 36% with median OS of 15.4 months was observed in the first-line setting, while in second or third line, both ORR and OS were less favorable at 22% and 7.6 months, respectively [Andre, T., et al 2004]. The use of taxane combinations in BTC have primarily been reported in small, nonrandomized studies [Sahai, V., et al 2018] [Tajima, H., et al 2017].

A particular phenotype called microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) found in several types of solid tumors is associated with increased mutation rate and genomic instability due to failure to repair the DNA mismatches that occur during normal DNA synthesis. A Phase 2 multicohort study evaluated the efficacy of pembrolizumab in the setting of MSI-H/dMMR tumors. The first cohort included MSI-H or dMMR metastatic colorectal cancer. The study was subsequently expanded to include 12

different tumor types with MSI-H or dMMR. A total of 86 participants were enrolled with objective radiographic responses in 53% of participants (46 of 86 participants; 95% CI, 42–64%), and 21% (n = 18) achieved a complete radiographic response [Le, D. T., et al 2017]. Responses were found to be durable and similar between colorectal cancer and other cancer subtypes. This led to approval of pembrolizumab by the FDA in May 2017 for adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. A number of other countries have approved pembrolizumab in a similar fashion.

There are also multiple studies evaluating the use of FOLFOX for the treatment of BTCs in second-line setting. A single-arm Phase 2 study involving 37 participants refractory to gemcitabine and cisplatin treated with FOLFOX reported an ORR of 21.6% and median time-to-progression (TTP) of 3.1 months (95% CI: 2.3-3.6) with a manageable AE profile [He, S., et al 2014]. A randomized Phase 3 study (ABC-06; NCT01926236) evaluating FOLFOX in second-line advanced BTC has completed enrollment and results are anticipated.

Targeted therapy options capable of advancing precision medicine for the treatment of BTC are currently being explored. Comprehensive genomic analysis of BTC with next generation sequencing has led to the identification and characterization of several genomic alterations as potential targets in distinct subgroups of BTC [Nakamura, H., et al 2015]. FGFR2 fusion, IDH1/2 and BAP1 mutations have been associated with intrahepatic CCA while PRKACA/PRKACB fusions, ELF3 and ARID1B are more specific for extrahepatic CCA. Gallbladder cancer has been shown to harbor EGFR, ERBB3, ARID2 and TERT promoter mutations [Nakamura, H., et al 2015] and HER2/neu mutations [Javle, M., et al 2015]. Clinical studies utilizing interventions targeting genomic alterations in BTC are ongoing. Overall, these alterations are seen in about 40% of biliary cancers, but individual alterations are limited to a small proportion of patients [Nakamura, H., et al 2015].

Locoregional therapies like hepatic arterial infusion radiofrequency ablation, transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) have also been used in patients with unresectable biliary cancer and liver predominant disease [Han, K., et al 2015]. There are no randomized controlled studies and most studies included a heterogenous, small group of participants without standardization of intervention modalities. Though some have reported encouraging results, there have been concerns about potential toxicity. Due to lack of validated data, these therapies are not considered as part of SOC.

Photodynamic therapy (PDT), a direct ablative technique using a photosensitizing agent, has also been of interest though more commonly used for palliation of biliary obstruction [Gao, F., et al 2010]. In patients with localized disease, liver transplant is a potential option for treatment. Some studies have reported improved outcome compared to surgical resection, however a direct comparison in randomized fashion has not been performed. With scarcity of donors, lack of Phase 3 studies, and a requirement for expertise, liver transplant has not been widely adopted [Banales, J. M., et al 2016] [Sapisochin, G., et al 2015]. External beam radiation and intraluminal brachytherapy have been used and reported in management of BTC for patients with localized disease. There is conflicting evidence of use of radiation

alone, but data with concurrent chemoradiation appear more promising. Small nonrandomized studies have reported improved outcomes with adjuvant concurrent chemoradiation [Kim, S., et al 2002] [Nakeeb, A. 2005]. In the adjuvant setting, the Phase 3 study PRODIGE 12-ACCORD 18 (UNICANCER GI group) showed participants with localized BTC that received GEMOX did not have statistically improved recurrence-free survival (RFS) compared to surveillance [Edeline, J., et al 2019]. In a Phase 3 study utilizing capecitabine as an adjuvant therapy in BTC (BILCAP), although an improvement in OS was reported, the primary endpoint of improving OS was not met [Primrose, J. N., et al 2019].

Although several studies are evaluating potential cytotoxic and molecularly targeted therapy options, the limitation of increased toxicity with cytotoxic chemotherapy and small selected populations for molecularly targeted therapy highlights the need for a more effective therapy than can be used for the majority of BTC patients. Current data support PD-1/PD-L1 mediated inhibition of adaptive immune response to carcinogenesis and, hence the role of checkpoint inhibition as a therapeutic option.

2.2.3 Rationale for Immunotherapy in Biliary Cancer: Preclinical and Clinical Studies

The PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in BTC. 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 demonstrated 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 (refer to the pembrolizumab IB).

As discussed, inflammation plays a key role in the development of BTC worldwide. The role of immune modulation and adaptive immune response to tumor antigens is an area of active research in variety of cancers including BTC. In a retrospective analysis of BTC, presence of tumor-infiltrating lymphocytes (TILs) was associated with improved outcome [Goeppert, B., et al 2013]. A total of 375 cases were analyzed, which included intra-/extrahepatic CCA and GBC. Of note, the presence of intraepithelial tumor-infiltrating CD4+, CD8+ and FoxP3+ TILs were associated with longer survival. This study also reported decline in adaptive immune response and increase in innate immune response components during dysplasia to primary carcinoma to metastases progression. Additionally, a large meta-analysis of 12 studies and over 2,000 participants showed similar results indicating association of improved clinical outcome with higher expression of TILs [Wang, Y., et al 2017]. These findings theorize evasion of immune surveillance and adaptive immune response in BTC and, hence, support the role of checkpoint inhibitor therapy in this patient population.

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

Single agent pembrolizumab has shown efficacy in several gastrointestinal tumors. Pembrolizumab has been approved by the FDA for PD-L1 + advanced refractory metastatic gastric cancer based on KEYNOTE-059 (NCT02335411) and hepatocellular cancer after progression on sorafenib based on KEYNOTE-224 (NCT02702414).

Early clinical studies have evaluated the prevalence of PD-L1 expression in BTC. KEYNOTE-028, a multicohort Phase 1b study, assessed pembrolizumab in PD-L1 positive solid tumors. This was a population with refractory disease and a large proportion (39.1%) had undergone ≥3 prior lines of therapy [Ott, P. A., et al 2018]. A total of 89 participants with advanced BTC were screened and 37 (42%) had PD-L1 positive tumors; of these, 24 participants were enrolled [Bang, Y. J., et al 2015], and data were reported for 23 participants [Ott, P. A., et al 2018]. In the BTC cohort, the median PFS was 1.8 months, and the median OS was 6.2 months. The 6-month and 12-month OS rates were 53% and 29%, respectively. The ORR (confirmed and unconfirmed) per RECIST 1.1 by investigator review was 17% (95% CI: 5%-39%) [Bang, Y. J., et al 2015] [Ott, P. A., et al 2018]. One response was a CR and 3 responses were PRs by investigator review (n=4). Across all cohorts in KEYNOTE-028, AEs were reported for 96% of the 475 participants treated with pembrolizumab. The AE profile was favorable, and only 4% of participants discontinued treatment due to an AE.

KEYNOTE-158 (NCT02628067) [Ueno, M., et al 2018] a Phase 2, multicohort study included participants with advanced BTC with prior progression or intolerance on standard chemotherapy. A total of 104 participants were enrolled, and among those, 61 had a tumor positive for PD-L1 expression (combined positive score [CPS] ≥1). Approximately half (52%) of participants had 2 or more prior lines of therapy. An overall response rate of 5.8% was noted with a DOR of >15 months in 2 participants. The median DOR was not reached. The median PFS was 2.0 months (95% CI: 1.9–2.1) and median OS was 9.1 months (95% CI: 5.6–10.4). Among participants with PD-L1 CPS ≥1, the ORR was 6.6 %, the median PFS was 2.1 months and the median OS was 9.6 months. Participants with CPS <1 had an ORR of 2.9%, median PFS was 1.9 months, and OS was 7.2 months. None of the participants were found to be microsatellite instability-high (MSI-H). The overall toxicity profile was manageable, and activity was seen regardless of PD-L1 status.

These data support modest efficacy of pembrolizumab monotherapy in advanced BTC.

2.2.4 Ongoing Clinical Studies in Biliary Cancer

Several other PD-1 and PD-L1 inhibitors are under investigation for BTC. Nivolumab is being evaluated as a single agent in the second-line setting (NCT02829918) in a Phase 2 study. Data from first 34 participants was reported. Out of 29 participants evaluable for response, 5 pts (17%) achieved PR and 11 pts (38%) achieved SD. The DCR was 55%. The

median PFS was 3.5 months [Kim, R., et al 2018]. At median follow-up of 8 months, OS had not been reached; the 6-month OS was 76.3%. In a Phase 1 study conducted in Japan, nivolumab in combination with gemcitabine and cisplatin in first-line was compared to single agent nivolumab in a refractory setting [Ikeda, M., et al 2019]. A total of 60 participants were enrolled, 30 participants in each cohort, and treatment was well tolerated in both cohorts. An ORR of 3.3% (90% CI: 0.7–13.6%) and a median OS of 5.2 months (90% CI: 4.5–8.7 months) was reported with nivolumab monotherapy. In the combination cohort, the ORR was 36.7% (90% CI: 23.9–51.7%) and the median OS was 15.4 months (90% CI: 11.8–Not estimable). Combination therapy seemed tolerable in this patient population with an expected adverse effect profile. In the combination arm, though a higher response rate was observed in the subgroup with PD-L1 expression ≥1% in tumor cells (n = 8), OS was better in the group with PD-L1 expression <1% in tumor cells (n = 21), however, due to the small number of participants, a reliable correlation could not be established with PD-L1 status.

A randomized Phase 2 study of nivolumab in combination with gemcitabine and cisplatin versus ipilimumab is ongoing with PFS as the primary endpoint (NCT03101566). Other agents under active investigation include durvalumab, tremelimumab and atezolizumab. A Phase 1 study from Asia evaluating durvalumab and durvalumab/tremelimumab combination included advanced BTC in an expansion cohort. Safety and efficacy data were reported after 107 participants were enrolled [Ioka, T., et al 2019]. A total of 42 participants were recruited to the durvalumab cohort followed by 65 participants in the durvalumab and tremelimumab combination group. Partial response was seen in 2/42 participants in the monotherapy group (4.8%) and 7/65 in the combination group (10.8%). Median OS was 8.1 months (95% CI, 5.6–10.1) for the monotherapy group and 10.1 months (95% CI, 6.2–11.4) for the combination group. The DOR was 9.6 months and 9.7 months for the 2 participants in the monotherapy group. The median DOR was 8.5 months for participants receiving combination therapy.

Atezolizumab is being studied in combination with pegvorhyaluronidase alfa (PEGPH20), cisplatin, and gemcitabine in a Phase 1b study in advanced biliary cancers. After enrollment of the first 48 participants, no significant toxicities were reported. One dose-limiting toxicity with febrile neutropenia was seen in the initial Run-in Phase.

2.2.5 Rationale and Safety of Combining Pembrolizumab with Gemcitabine and Cisplatin

Cisplatin-based combination chemotherapy with gemcitabine is the standard first-line treatment in the US (NCCN Guidelines), Japan (Japanese Society of Hepato-Biliary-Pancreatic Surgery guidelines), Europe (ESMO guidelines) and several other countries worldwide for patients with advanced or unresectable BTC. Several lines of evidence support the rationale to add pembrolizumab therapy to gemcitabine/cisplatin. First, gemcitabine has been shown to lead to immunogenic cell death. However, gemcitabine may have additive/synergistic effects with anti-PD-L1. Despite modest single agent activity, and a reduction in the levels of activated intratumoral CD8+ T-cells, combination of gemcitabine and anti-PD-L1 treatment resulted in enhanced antitumor responses with 40% CRs [Cubas, R., et al 2018]. There is no antagonistic effect of gemcitabine/cisplatin in combination with concurrent pembrolizumab. Phase 2 combination of ipilimumab with gemcitabine/cisplatin in

bladder cancer has shown in pharmacodynamic (PD) data that the addition of ipilimumab leads to immunostimulatory effects in circulating cells, suggesting that chemotherapy may not necessarily abrogate immune effects of checkpoint blockade [Galsky, M. D., et al 2018].

Additionally, Phase 1 combinations of an immune checkpoint inhibitor therapy with platinum-containing doublet chemotherapy have been reported to show tolerability in NSCLC [Papadimitrakopoulou, V., et al 2015]. In metastatic NSCLC, a Phase 3 study KEYNOTE-189 shown that treatment with pembrolizumab, pemetrexed, and platinum resulted in significantly longer OS and PFS than pemetrexed plus platinum alone in the first-line setting. Additionally, KEYNOTE-407 shown that pembrolizumab in combination with chemotherapy (carboplatin and either paclitaxel or nab-paclitaxel) led to an improvement in OS, PFS and ORR when compared to chemotherapy alone in first-line metastatic NSCLC. KEYNOTE-048 (NCT02358031) and KEYNOTE-059 (NCT02335411) have been investigating the addition of pembrolizumab to chemotherapy in head and neck cancer, and gastric cancer, respectively. Early reports from KEYNOTE-059 have shown manageable toxicities [Bang, Y. J., et al 2019]. KEYNOTE-361 is a randomized, open label, Phase 3 study of pembrolizumab with or without chemotherapy versus chemotherapy alone in participants with advanced urothelial carcinoma. CCI

CCI

Nivolumab with gemcitabine and cisplatin has been evaluated in BTC in a Phase 1 study involving 2 patient cohorts [Ikeda, M., et al 2019]. Participants refractory or intolerant to gemcitabine/cisplatin were treated with nivolumab monotherapy and therapy naïve participants were treated with nivolumab in combination with gemcitabine and cisplatin in the first-line setting. A total of 60 participants were enrolled, 30 participants in each cohort and the AE profile was manageable in both cohorts. An ORR of 3.3% (0.7-13.6) and a median OS of 5.2 months (4.5-8.7) was reported with nivolumab monotherapy. In the combination cohort the ORRs were 36.7 % (23.9-51.7) and the median OS was 15.4 months (11.8-Not estimable) [Ueno, M., et al 2019]. In a study evaluating nivolumab monotherapy in participants in China with metastatic BTC treated in a nonclinical trial setting at a hospital, the median PFS was reported as 3.1 months (95% CI: 2.13–4.06 months) [Gou, M., et al 2019]. One participant (3.3%) achieved CR, 5 (16.7%) achieved PR, 12 (40%) were SD, and 12 (40%) were PD. The ORR and DCR were 20% and 60%, respectively, and the OS was not reported.

In summary, there are early phase data supporting safety and modest efficacy of pembrolizumab monotherapy in advanced BTC (KEYNOTE-158 and KEYNOTE-028), as well as studies showing safety and efficacy of pembrolizumab plus platinum chemotherapy combinations in several cancers including biliary, head and neck, lung and bladder cancers. The present randomized Phase 3 study has been designed to investigate the use of pembrolizumab in first-line setting in combination with SOC cytotoxic chemotherapy for potential additive or synergistic therapeutic advantage. The primary study hypothesis is that combination therapy (pembrolizumab + chemotherapy) is superior to chemotherapy only with respect to OS in nonbiomarker selected participants. A similar Phase 2 study involving

50 participants with advanced CCA in combination with the same chemotherapy (gemcitabine/cisplatin) is planned in collaboration with European Organization for Research and Treatment of Cancer (EORTC). Any early data about unexpected toxicity or efficacy seen in this study will be used for future considerations in the proposed study.

2.2.6 Delayed Treatment Effect With Immunotherapy

Immune agents like checkpoint inhibitors have an indirect mechanism of action on tumor cells unlike standard chemotherapeutic agents and hence may have a delay in treatment effect. Although not universal, delayed treatment effect has been observed in several studies evaluating immunotherapy. In a first-line study of melanoma comparing ipilimumab plus dacarbazine versus placebo plus dacarbazine, overall survival benefit was observed after the initial 4 months as seen in delayed separation of the survival curve [Robert, C., et al 2011]. In CheckMate 057, a study of nivolumab versus docetaxel for previously treated metastatic nonsquamous nonsmall-cell lung cancer, the experimental arm with immunotherapy was actually worse initially with subsequent improvement. The study led to FDA approval of nivolumab for metastatic nonsquamous non-small cell lung cancer after prior platinum-based chemotherapy [Kazandjian, D., et al 2016]. More recently, delayed separation of survival curves was seen in KEYNOTE-048, a Phase 3 study of pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck [Burtness, B., et al 2019]. Other examples include IMpower 133 [Horn, L., et al 2018], IMpower 150 [Socinski, M. A., et al 2018], and KEYNOTE-062 [Shitara, K., et al 2020].

In summary, delayed treatment effect has been noted with immunotherapy and may have a significant impact on statistical design and results of clinical studies with these agents. It would be prudent to account for delayed effect in the study design to make it more applicable to such agents and avoid stopping a study with a potentially effective regimen based on early results.

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 combination with chemotherapy in advanced and/or unresectable BTC population is unknown since these participants have not been previously studied with this combination. 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, 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.

Based on pembrolizumab chemotherapy combination data from other indications and from data in early phase studies with BTC treated with pembrolizumab, a favorable benefits-risk profile is anticipated.

Participants in clinical studies generally cannot expect to receive direct benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. However, experience with this drug in combination with chemotherapy approved in other indications, 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 first-line therapy for participants with advanced and/or unresectable biliary tract carcinoma:

Although the original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, throughout this protocol, the term RECIST 1.1 refers to an adjustment of RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. Refer to Section 4.2.2.2 for further details.

Objectives	Endpoints
Primary	
• Objective: To compare overall survival (OS) between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin • Hypothesis (H1): Pembrolizumab plus gemcitabine/cisplatin is superior to placebo plus gemcitabine/cisplatin with respect to OS	• OS: the time from randomization to death due to any cause
Secondary	
• Objective: To compare progression-free survival (PFS) per RECIST 1.1 as assessed by blinded independent central review (BICR) between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin • Hypothesis (H2): Pembrolizumab plus gemcitabine/cisplatin is superior to placebo plus gemcitabine/cisplatin with respect to PFS per RECIST 1.1 by BICR	• PFS: the time from randomization to the first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first

Objectives	Endpoints
• Objective: To compare objective response rate (ORR) per RECIST 1.1 as assessed by BICR between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin • Hypothesis (H3): Pembrolizumab plus gemcitabine/cisplatin is superior to placebo plus gemcitabine/cisplatin with respect to ORR per RECIST 1.1 as assessed by BICR	• Objective Response (OR): complete response (CR) or partial response (PR)
• Objective: To evaluate duration of response (DOR) per RECIST 1.1 as assessed by BICR	• DOR: for participants who show confirmed CR or PR, the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first
• Objective: To evaluate the safety and tolerability profile of pembrolizumab plus gemcitabine/cisplatin	• Adverse events (AEs) • Study intervention discontinuations due to AEs
Tertiary/Exploratory	
• Objective: To evaluate disease control rate (DCR) per RECIST 1.1 as assessed by BICR	• Disease Control (DC): a best overall response of CR, PR, or stable disease (SD). SD must be achieved at ≥6 weeks after randomization to be considered best overall response
• Objective: To evaluate efficacy outcomes per RECIST 1.1 modified for immune-based therapeutics (iRECIST) as assessed by the investigator	• PFS, OR, DOR, DC
• Objective: To evaluate efficacy outcomes per RECIST 1.1 as assessed by the investigator	• PFS, OR, DOR, DC
• Objective: To compare PFS and ORR per RECIST 1.1 as assessed by BICR and OS by PD-L1 status (CPS ≥1 versus <1, and additional cutoff ≥10) between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin	• PFS, OR, OS

Objectives	Endpoints
• To evaluate PFS per RECIST 1.1 as assessed by BICR and OS by MSI status	• PFS, OS
• Objective: To identify molecular CCI [redacted] CCI [redacted] plus gemcitabine/cisplatin	• CCI [redacted]
• Objective: To compare time to deterioration (TTD) and score change from baseline in global quality of life using the EORTC Quality of Life (QOL) Questionnaire (EORTC QLQ) -C30 and EORTC QLQ-BIL21 between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin	• Scores from the global health status/QOL scale on the EORTC QLQ-C30 and EORTC QLQ- BIL21 • TTD: the time to first onset of a 10 point or more decrease from baseline. TTD evaluated for EORTC QLQ-C30 and EORTC QLQ-BIL21 global health status/QOL
• 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
• Objective: CCI [redacted] CCI [redacted] CCI [redacted] of adverse events	• CCI [redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double blind study of pembrolizumab plus gemcitabine/cisplatin versus placebo plus gemcitabine/cisplatin in participants with advanced (metastatic) and/or unresectable (locally advanced) biliary tract carcinoma (intra- or extrahepatic cholangiocarcinoma or gallbladder). Participants must have measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, as determined by investigator/site radiologist. Lesions situated in a previously irradiated area by either radiotherapy, photodynamic therapy, or arterial embolization are considered measurable if progression has been shown in such lesions. Other key eligibility criteria include no prior systemic therapy, and an ECOG performance scale (PS) score of 0 or 1.

Approximately 1048 participants are expected to be randomized 1:1 into 1 of the 2 treatment arms:

Arm A:

Pembrolizumab 200 mg IV on Day 1 Q3W + gemcitabine 1000 mg/m^2 IV and cisplatin 25 mg/m^2 IV on Day 1 and Day 8 Q3W.

Arm B:

Placebo (saline) IV on Day 1 Q3W + gemcitabine 1000 mg/m^2 IV and cisplatin 25 mg/m^2 IV on Day 1 and Day 8 Q3W.

Eligible participants will be stratified by 1) Region (Region 1: Asia versus Region 2: Non-Asia), 2) locally advanced versus metastatic, and 3) site of origin (gallbladder, intrahepatic, or extrahepatic).

After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until approximately 158 participants in China have been enrolled to meet local regulatory requirements. An extension portion of the study will be identical to the global portion (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, and study procedures) in general, with the exception of an additional statistical analysis plan for China participants. Details of the analysis will be provided in a separate supplemental statistical analysis plan (sSAP).

This protocol does not allow participants to cross over between arms. During the initial intervention phase, cisplatin is given for a maximum of 8 cycles. Pembrolizumab or placebo will continue until up to 35 administrations, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of study intervention, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with study intervention or procedure requirements, or administrative reasons. Gemcitabine will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of study intervention, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with study intervention or procedure requirements, or administrative reasons.

Participants in Arm A who stop study intervention after achieving SD or better may be eligible to receive additional pembrolizumab for up to 17 cycles if they experience radiographic disease progression while off study intervention, according to the criteria in Section 6.1.2. Gemcitabine may be continued until PD or unacceptable toxicity during second course at investigator's discretion. This retreatment is termed the Second Course Phase of this study. Participants are unblinded individually upon disease progression while off study intervention, and are able to participate in the Second Course Phase only if they were receiving pembrolizumab originally, and if the study remains open. An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis in this study. The decision to re-treat

will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of study intervention and the participant still meets the safety parameters listed in the inclusion/exclusion criteria (refer to Sections 5.1 and 5.2 for further details). During this phase, the participant may resume the same previously administered systemic cytotoxic chemotherapy at the discretion of the local site investigator.

The primary endpoint in this study is OS.

Adverse events 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 5.0.

The first on treatment imaging assessment will be performed at 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed Q6W (42 days ±7 days) through Week 54 and Q12W (84 days ± 7 days) thereafter. Progressive disease will be verified by BICR per RECIST 1.1 and may be further confirmed at the site by subsequent imaging per iRECIST. Refer to Section 8.2.1 for details about tumor imaging and assessments.

After verification of progression by BICR per RECIST 1.1 and/or initiation of a subsequent anticancer treatment, all participants will be followed for survival until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever comes first.

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

There are interim efficacy/immunogenicity analyses in this study. Details of these interim analyses are described in Section 9.

4.2 Scientific Rationale for Study Design

This study is designed as a double blind placebo-controlled study evaluating addition of pembrolizumab to the SOC chemotherapy combination of gemcitabine and cisplatin. The experimental arm (Arm A) consists of chemotherapy with pembrolizumab, and the comparator arm (Arm B) consists of chemotherapy with placebo. The use of a placebo control with pembrolizumab will allow unbiased evaluation of this novel combination therapy. Additionally, pembrolizumab in combination with gemcitabine and cisplatin is currently being evaluated in participants with advanced urothelial carcinoma. The adverse event profile of the combination of pembrolizumab with chemotherapy has been generally comparable to chemotherapy alone. This allows blinding to be an appropriate strategy for evaluation of the combined activity in this population with few options for treatment.

4.2.1 Rationale for Stratification Factors

Geographic region stratification includes 2 categories: a) Asia b) Non-Asia. Because of known ethnic differences in incidence, clinical practice, primary tumor location, and prognosis of BTC, stratification of geographic region is required to get equal distribution of treatment groups in different populations.

Presentation with locally advanced disease, which is unresectable, versus Stage IV disease with distant organ metastatic involvement has been shown to have significant impact on clinical outcome and, hence, is used for stratification to ensure balance between treatment arms.

Location of tumor is an important consideration as the subtypes of BTC (gallbladder/intrahepatic/extrahepatic bile duct cancers) are distinct biological entities based on molecular characterization and clinical behavior. Site of origin has been used as a stratification factor in a number of studies involving BTC including ABC-02 [Valle, J., et al 2010]. Additionally, based on next generation sequencing data, there is variability in these subtypes with respect to actionable mutations [Nakamura, H., et al 2015] [Shibata, T., et al 2018] [Chan-On, W., et al 2013] [Javle, M., et al 2015] and potential targeted therapy options.

4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

This study will use OS as the primary endpoint.

The endpoint of OS is the gold standard for demonstrating superiority of antineoplastic therapy in clinical studies. In biliary tract cancer, life expectancy is short and hence OS as a sole primary endpoint is feasible. Additionally, PFS improvement in the absence of OS may not be clinically meaningful, supporting OS as a sole primary endpoint and PFS, OR, and DOR as secondary endpoints. Progression-free survival as a secondary endpoint is an acceptable measure of clinical benefit for a late stage study that shows superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be submitted to an imaging CRO (iCRO) and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression, as determined by central review, will be communicated to the site.

OR is an acceptable measure of clinical benefit for a late stage study that shows superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. Images will be read per RECIST 1.1 by BICR to minimize bias in the response assessments.

DOR per RECIST 1.1, assessed by BICR, will serve as an additional measure of efficacy and is a commonly accepted endpoint by both regulatory authorities and the oncology community.

4.2.2.2 RECIST 1.1

RECIST 1.1 will be used when assessing images for efficacy measures. Although the original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

4.2.2.3 iRECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (refer to Section 8.2.1.6). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

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

4.2.2.4 Safety Endpoints

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

4.2.2.5 Patient-reported Outcomes

The EORTC QLQ-C30, EuroQoL-5D-5L (EQ-5D-5L), and EORTC QLQ-BIL21 patient-reported outcomes (PROs) are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.2.5.1 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]. It is scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). The EORTC QLQ-C30 global health status/QOL scale uses a 7-point scale scoring with anchors (1=very poor and 7=excellent). The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QOL in oncology studies [Aaronson, N. K., et al 1993].

4.2.2.5.2 EuroQoL 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. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.2.5.3 EORTC QLQ-BIL21

The EORTC QLQ-BIL21 is a validated questionnaire for the assessment of QOL in patients with CCA and GBC. The EORTC QLQ-BIL21 consists of 21 questions. Three single items assess treatment side effects, difficulties with drainage bags/tubes and concerns regarding weight loss. Eighteen items are grouped into 5 scales: eating symptoms (4 items), jaundice symptoms (3 items), tiredness (3 items), pain symptoms (4 items) and anxiety symptoms (4 items). The response is provided on a 4-point Likert scale.

4.2.2.6 Pharmacokinetic Endpoints

Based on pharmacokinetic (PK) data obtained in this study and from other studies, observed pembrolizumab data coadministered with gemcitabine/cisplatin will be compared to historical monotherapy pembrolizumab PK data to support the proposed dosing regimen. Blood samples will also be obtained to measure antidrug antibodies (ADA) of pembrolizumab. Simultaneous PK sampling is required for interpretation of ADA analysis.

4.2.2.7 Planned Exploratory Biomarker Research

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

4.2.2.8 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include CCI [redacted] CCI [redacted] CCI [redacted] depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is CCI [redacted] CCI [redacted] CCI [redacted] The

4.2.3 Rationale for the Use of Comparator/Placebo

In this study, all participants will receive the current SOC, gemcitabine and cisplatin. Participants will be randomized at enrollment to the pembrolizumab or placebo plus gemcitabine/cisplatin. Intervention groups are expected to receive 35 administrations of pembrolizumab or placebo (approximately 2 years). Placebo will be normal saline solution prepared by the local unblinded pharmacist, dosed and administered in the same manner as the investigational product. The Phase 3 ABC-02 study has established the gemcitabine/cisplatin combination as a SOC for BTC for patients with ECOG PS 0 or 1, achieving a median survival close to a year (11.7 months) for gemcitabine/cisplatin, compared with 8.1 months for gemcitabine alone (HR 0.64, 95% CI: 0.52-0.80; p <0.001) [Valle, J., et al 2010] with a similar benefit in the randomized Phase 2 Japanese study, BT22 [Okusaka, T., et al 2010]. 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 SOC for patients with BTC.

4.3 Justification for Dose

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

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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose.

Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

Gemcitabine at 1000 mg/m^2 and cisplatin at 25 mg/m^2 are administered on Day 1 and Day 8 of a 21-Day cycle. This dose of gemcitabine/cisplatin was used in the ABC-02 study, which defined gemcitabine/cisplatin as the SOC for advanced BTC. Based on global clinical practice patterns, gemcitabine will be administered until PD or unacceptable toxicity, cisplatin will be administered for a maximum of 8 cycles.

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.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Participants with advanced and/or unresectable hepatobiliary carcinoma will be enrolled in this study.

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has histologically confirmed diagnosis of advanced (metastatic) and/or unresectable (locally advanced) biliary tract cancer (intra-or extrahepatic cholangiocarcinoma or gallbladder cancer).

2. Has measurable disease based on RECIST 1.1, as determined by the site investigator. Lesions situated in a previously treated area by either radiotherapy, photodynamic therapy, or arterial embolization are considered measurable if progression has been shown in such lesions and they meet criteria for measurable disease per RECIST 1.1.

3. Participants with past or ongoing HCV infection are eligible for the study. CCI
CCI

4. Participants with controlled hepatitis B are eligible for the study, as long as they meet the following criteria:

- CCI
-

Demographics

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

Male Participants

6. Male participants are eligible to participate if they agree to the following during the intervention period and for at least and through 180 days after the last dose of chemotherapy:

- Refrain from donating sperm

PLUS either:

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

OR

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

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

- Male participants must also agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

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

Female Participants

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

- Is not a woman of childbearing potential (WOCBP)

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least and through 210 days after the last dose of chemotherapy or through 120 days after the last dose of pembrolizumab or placebo, whichever is greater, and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours (urine) or 72 hours (serum) before the first dose of study intervention.

    Note: If 24 hours (for urine) or 72 hours (for serum) have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.

Note: In regions where required via documented regulatory request (and subsequently approved by the Sponsor), pregnancy tests within 24 hours prior to treatment allocation will be required.

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

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

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

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

Informed Consent

8. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the study without participating in future biomedical research.

Additional Categories

9. Have a performance status of 0 or 1 on the ECOG performance scale within 3 days prior to the first dose of study intervention.

10. Provide archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (ie, obtained for histological confirmation) for biomarker analysis. The tumor tissue must be received by the central vendor and be deemed adequate for biomarker analysis evaluation, including but not limited to PD-L1 and MSI biomarker analysis, prior to participant randomization. Formalin-fixed, paraffin-embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

    Note: Details pertaining to tumor tissue submission can be found in the laboratory manual.

11. Have a life expectancy of greater than 3 months.

    Note: Participants with malignant ascites at baseline will be excluded.

12. Have adequate organ function, as defined in the following table (Table 3). Specimens must be collected within 14 days prior to the first dose of study intervention.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance	≤1.5 × ULN OR ≥60 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); 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 using the Cockcroft-Gault Method: Refer to Appendix 10 for appropriate calculation. Refer to Section 6.6.2.2 for CrCl requirement prior to administration of first dose of cisplatin.

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

5.2 Exclusion Criteria

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

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

Medical Conditions

1. Has had previous systemic therapy for advanced (metastatic) or unresectable (locally advanced) biliary tract cancer (intra-or extra hepatic cholangiocarcinoma or gallbladder cancer), with the exception of neoadjuvant/adjuvant therapy which is allowed.

Neoadjuvant/adjuvant therapy should have been completed at least 6 months prior to diagnosis of advanced and/or unresectable disease, and participants should not have received gemcitabine and/or cisplatin in the neoadjuvant/adjuvant setting. Participants who received prior neoadjuvant/adjuvant therapy with R2 postoperative pathology of the oncologic resection are excluded.

2. Has ampullary cancer.

3. Has small cell cancer, neuroendocrine tumors, lymphoma, sarcoma, mixed tumor histology and/or mucinous cystic neoplasms.

   Note: Participants with mixed HCC/cholangiocarcinoma may be included.

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

5. Has undergone major surgery and has not recovered adequately from the procedure and/or complications from the surgery prior to starting study intervention.

6. A WOCBP who has a positive urine pregnancy test within 24 hours prior to administration of study intervention (see inclusion criterion 7 and Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

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

8. Has received prior anticancer therapy (eg, TACE, palliative surgery) for advanced unresectable biliary tract cancer (intra-or extra hepatic cholangiocarcinoma or gallbladder cancer), including investigational agents within 4 weeks prior to randomization.

9. Has not recovered (ie, AE ≤Grade 1 or baseline) from AEs due to previously administered anticancer therapy. Participants with ≤Grade 2 neuropathy may be eligible based on investigator assessment.

10. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and have not had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to noncentral nervous system (CNS) disease if deemed safe by the investigator. A 2-week washout period is required for a longer course of radiation (>2 weeks).

11. Has received a live vaccine within 30 days prior to the first dose of study intervention.

    Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, *Bacillus* Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

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

14. Has a known additional invasive malignancy that is progressing or has required active treatment within the past 3 years.

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

15. Has severe hypersensitivity (≥Grade 3) to pembrolizumab, gemcitabine, or cisplatin and/or any of their excipients.

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

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

18. Has dual active HBV infection CCI [redacted] and HCV infection CCI [redacted] at study entry.

19. Has a known history of human immunodeficiency virus (HIV) infection.

    Note: No HIV testing is required unless mandated by local health authority.

20. Has known active tuberculosis (TB; *Bacillus tuberculosis*). Note: No testing for TB is required unless mandated by local health authority.

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

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

23. 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

24. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 180 days (male participants) or 210 days (female participants) after the last dose of chemotherapy or through 120 days (female participants only) after the last dose of pembrolizumab or placebo, whichever is greater.

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

5.3 Lifestyle Considerations

There are no lifestyle considerations defined for this study.

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.

Rescreening is allowed in case of screen failure. Please refer to Section 8.11.1 - Screening for details.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 4.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admini-stration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Arm A	Experimental	Pembrolizumab	Drug	Sterile Suspension (Vial)	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle, up to 35 admini-strations	Experimental	IMP	Central
Arm A	Experimental	Cisplatin	Drug	Vial	1 mg/mL vial, 20 mg vial, or 50 mg vial	25 mg/m^2	IV Infusion	Day 1 and Day 8 of each cycle, up to 8 cycles	Background Treatment	NIMP	Local or Central
Arm A	Experimental	Gemcitabine	Drug	Vial	1 g/ vial	1000 mg/m^2	IV Infusion	Day 1 and Day 8 of each cycle, until PD or unacceptable toxicity	Background Treatment	NIMP	Local or Central
Arm B	Active Comparator	Placebo (Normal Saline)	Drug	Sterile Suspension (Vial)	N/A	N/A	IV Infusion	Day 1 of each cycle, up to 35 admini-strations	Placebo	IMP	Local
Arm B	Active Comparator	Cisplatin	Drug	Vial	1 mg/mL vial, 20 mg vial, or 50 mg vial	25 mg/m^2	IV Infusion	Day 1 and Day 8 of each cycle, up to 8 cycles	Background Treatment	NIMP	Local or Central
Arm B	Active Comparator	Gemcitabine	Drug	Vial	1 g/ vial	1000 mg/m^2	IV Infusion	Day 1 and Day 8 of each cycle, until PD or unacceptable toxicity	Background Treatment	NIMP	Local or Central

Arm Name	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admini-stration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed. Refer to Section 10.7 (Appendix 7) for country-specific requirements.											

All study interventions will be administered on an outpatient basis.

All products indicated in Table 4 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.

6.1.1 Treatment

The initial treatment or first course of pembrolizumab consists of 35 treatments. Note: The number of treatments is calculated starting with the first dose.

For participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab or placebo beyond the initial CR confirmation date, treatment may be stopped.

These participants may be eligible for Second Course described in Section 6.1.2.

6.1.2 Second Course

All participants who have SD, PR, or CR may be eligible for up to an additional 17 cycles of pembrolizumab if there is BICR-verified radiographic disease progression by RECIST 1.1 after initial treatment or first course has been completed or stopped for confirmed CR as specified in Section 6.1.1 after consultation with the Sponsor. This retreatment is the Second Course of this study.

Participants may enter the Second Course if all of the following criteria are met:

- The participant received pembrolizumab, determined upon unblinding if applicable
- No new anticancer treatment was administered after the last dose of study intervention
- The participant meets all of the inclusion criteria and none of the exclusion criteria
- The study is ongoing

The decision of whether or not to continue gemcitabine during second course will be at the discretion of the investigator. If continued, participants will be retreated at the same dose level and frequency as when they last received the combination of pembrolizumab and gemcitabine. Treatment with gemcitabine will continue until PD or intolerable toxicity.

An objective response or disease progression that occurs during the Second Course will not be counted as an event for the primary analysis in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab or placebo are provided in the Pharmacy Manual. Dose preparation must be performed by separate unblinded study personnel. Dose administration must be performed by blinded study personnel.

Gemcitabine and cisplatin will be prepared and administered as per local product label/SmPC. The body surface area (BSA) in m^2 should be calculated per local guidance. The dose of gemcitabine and cisplatin shall not be recalculated by body weight fluctuation in principle, but for 10% or higher fluctuation of body weight, recalculation is possible at the discretion of the investigator. When recalculating, BSA in m^2 should be calculated per local guidance.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to (Arm A) pembrolizumab plus gemcitabine/cisplatin and (Arm B) placebo plus gemcitabine/cisplatin.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

- Region (Region 1: Asia versus Region 2: Non-Asia)
- Locally Advanced versus Metastatic
  - Note: In the event the participant has locally advanced and metastatic BTC, the participant should be stratified as metastatic.
- Site of Origin (gallbladder/intrahepatic/extrahepatic)

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Administration of study intervention(s) will be monitored by the investigator and/or study staff, and/or qualified designee per institutional guidelines and procedures. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

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

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for non-hepatic 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 intervention may be required. The investigator is to discuss any prohibited medication/vaccination 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.

Listed below are concomitant therapies that should be avoided or carefully monitored:

- Hepatotoxic drugs (examples below):
  - Etifoxine
  - Isoniazid
  - Nitrofurantoin
  - Ketoconazole
  - Amiodarone
  - Phenytoin
- Herbal supplements or alternative medicines should also be avoided during the Screening and Intervention Phase of this study.
- Possible interaction between gemcitabine and warfarin has been reported and may occur at any time. Close monitoring is recommended (monitor INR weekly during gemcitabine treatment and for 1 to 2 months after discontinuing gemcitabine treatment).
- Any use of other myelosuppressive medications should be carefully monitored for risk of infection.
- Participants with controlled hepatitis B enrolled in the study may require close monitoring of liver function tests and other parameters for hepatitis reactivation if they are exposed to prolonged corticosteroids, anti-tumor necrosis factor (TNF) therapy or other immunosuppressive therapy for management of irAEs.
- Untreated or incompletely treated HCV participants may initiate antiviral therapy for HCV if liver function remains stable for at least 3 months on study intervention.
- For HBV viral load over 100 IU/mL during study intervention, participants must start treatment for HBV.

Listed below are concomitant therapies prohibited during the course of 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

  Note: Radiation therapy to a symptomatic lesion or to the brain is allowed at the Investigator's discretion. Radiation therapy to 2 symptomatic lesions may be allowed following Sponsor Consultation. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease if deemed safe by the investigator. A 2-week washout period is required for a longer course of radiation (>2 weeks).

- 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.

  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.

- Any medication prohibited in combination with chemotherapy as described in the respective product labels for cisplatin and gemcitabine.
- Any chronic immunological-suppressive treatment for any reason other than the management of AEs, as described in Section 6.6.1 (Table 5).

  Note: Systemic glucocorticoids are permitted only for the following purposes:

  - To modulate symptoms of an AE that is suspected to have an immunologic etiology

- As needed for the prevention of emesis; systemic steroid use as antinausea medication should be limited as deemed safe by the investigator due to possible theoretical risk of lower efficacy of pembrolizumab
- Premedication for IV contrast allergies
- Short-term oral or IV use in doses >10 mg/day prednisone equivalent for chronic obstructive pulmonary disease exacerbations
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

In addition, the following glucocorticoid use is allowed:

- For topical or ocular use
- Intraarticular joint use
- For inhalation in the management of asthma or chronic obstructive pulmonary disease.

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

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. If participants experience an SAE or ECI, all concomitant medications administered more than 30 days after the last dose of study intervention are to be recorded for SAEs and ECIs as defined in Section 8.4.

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

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

guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or placebo.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab or placebo, the investigator does not need to follow the treatment guidance. Refer to Table 5 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification (Escalation/Titration/Other)

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

If appropriate, the investigator may attribute each toxicity event to gemcitabine, cisplatin, pembrolizumab or placebo and use dose modification according to Table 5 and Table 6. (pembrolizumab) and Table 7 (gemcitabine/cisplatin). To ensure that participants can receive adequate SOC chemotherapy dosing, standard supportive care measures should be used first, before dose modification, if there are no other reasons to modify SOC dosing for chemotherapy agents. Dose modification should be performed considering the following:

- Treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to the guideline for restarting each study intervention.

- Pembrolizumab or placebo dose reductions are not permitted. Pembrolizumab or placebo treatment may be interrupted or discontinued due to toxicity.

- Chemotherapy may be interrupted for a maximum of 6 weeks from last dose in case of chemotherapy-related toxicity; pembrolizumab or placebo may be interrupted for a maximum of 12 weeks from last dose (refer to Section 6.6.1.1).

- If a participant experiences several toxicities related to chemotherapy (gemcitabine and/or cisplatin) and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

- Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the study interventions. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, chemotherapy should be reduced, interrupted, or discontinued, and pembrolizumab or placebo should be interrupted or discontinued according to the recommended dose modifications. Both groups may have one or both chemotherapy agents discontinued and continue to receive pembrolizumab or placebo. The reverse is also allowed, ie, pembrolizumab or placebo can be stopped but one or both chemotherapy agents continued if the investigator attributes the AE to pembrolizumab or placebo.

The CTCAE v5.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification.

If toxicity is not otherwise specified, investigators should refer to the product label or local guidelines for dose adjustments.

In addition, participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures are included in Table 6 (pembrolizumab), Table 7 (gemcitabine/cisplatin) and Section 6.5.1.

6.6.1.1 Dose Modification of Pembrolizumab

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.

Dose Modification and Toxicity Management Guidelines for Non-hepatic irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

For guidance related to the diagnosis and management of hepatic ECIs, refer to Section 6.6.2.3. Refer to Section 10.7 (Appendix 7) for country-specific requirements.

Table 5 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 (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations 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 monotherapy, coformulations, or IO combinations associated infusion reactions are provided in Table 6.

Table 6 Pembrolizumab Monotherapy, Coformulations, or IO Combinations Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction: infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 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 after 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 intervention.	No subsequent dosing

h=hour; IV=intravenous; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.

Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

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

6.6.1.2 Dose Modification of Gemcitabine or Cisplatin

Dose modifications for gemcitabine and cisplatin are detailed in Table 7. **The following serves as a guide and does not replace investigator's clinical judgment. Follow local applicable product label recommendations if dosing considerations are more stringent.**

- CrCl will be based on the original weight-based Cockcroft and Gault formula (Appendix 10). If the calculated CrCl is <60 or >120 mL/min, measure EDTA clearance or CrCl before prescribing. CrCl must be ≥60 mL/min prior to administration of first dose of cisplatin and ≥40 mL/min prior to the administration subsequent doses of cisplatin. Cisplatin may be delayed for up to 42 days to allow the participant time to recover from the cisplatin-related toxicity. If a participant's CrCl value has not returned to ≥40 mL/min within 42 days after the previous dose, cisplatin must be discontinued. Additional details for dose modifications for cisplatin use are listed in Table 7.

- Gemcitabine should be administered with caution in participants with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations. For significant renal impairment defined as CrCl <30 mL/min, consider dose reduction and discuss with Sponsor. For serum bilirubin >1.6 mg/dL, consider dose reduction of gemcitabine to 800 mg/m^2. Monitor carefully and discontinue gemcitabine if any drug-related worsening occurs [Venook, A. P., et al 2000].

- Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia, such as rapidly falling hemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of hemolytic uremic syndrome. Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required.

- Maximal dose reduction permitted is up to 40% of starting dose of cisplatin (10 mg/m^2) and gemcitabine (400 mg/m^2). Doses below this level are not considered therapeutic and the participant will be discontinued from the related chemotherapy.

Table 7 Dose Modification Guidelines for Gemcitabine/Cisplatin-related Adverse Events

Category	Toxicity	Grade	Gem dose	Cis dose	Timing for Restarting Study Intervention	Subsequent Dose
Hematologic[a]	Neutrophil count decreased[b]	1-2[b]	None	None	N/A	N/A
		3	75%	None	N/A	Gemcitabine dose should be re-escalated to full dose (100%) on the subsequent cycles upon recovery of hematologic toxicity. If reduction required for 2 consecutive doses, permanently reduce dose of gemcitabine by 25%[d]
		4[c]	Hold	Hold	Neutrophil count recovers to >1000/mm^3 [d]	Reduce gemcitabine dose by 25% of last dose[d,e]
	Febrile Neutropenia[b]	3-4[c]	Hold	Hold	Toxicity resolves and Neutrophil count recovers to >1000/mm^3 [d]	Reduce gemcitabine dose by 25% of last dose[d,e]
	Platelet count decreased	3	75%	100%	N/A	Gemcitabine dose should be re-escalated to full dose (100%) on the subsequent cycles. If reduction is required for 2 consecutive doses, permanently reduce gemcitabine dose by 25%[d]
		4[c]	Hold	Hold	Platelet count recovers to >50,000/mm^3 [d]	Reduce gemcitabine dose by 25% of last dose[d,e]

Category	Toxicity	Grade	Gem dose	Cis dose	Timing for Restarting Study Intervention	Subsequent Dose
Non-hematologic[a]	Renal dysfunction	Serum creatinine increased above baseline	100%[f]	Subsequent dosing based on CrCl (mL/min)[g] <u>Cisplatin Dose:</u> **>60:** Give 100%, **51– 60:** Give 75%, **40 – 50:** Give 50%, **<40 mL/min:** Hold and follow modifications above on recovery and if not recovered to at least ≥40 mL/min within 42 days after the previous dose permanently discontinue		
	Peripheral Sensory Neuropathy[h]	2	100%	75%	N/A	Reduce cisplatin dose by 25% of last dose
		3[c]	100%	Hold	Toxicity resolves to ≤Grade 2[a]	Reduce cisplatin dose by 25% of last dose. Continue to reduce cisplatin by 25% for each additional episode.
		4	100%	N/A	N/A	Permanently discontinue
	Nausea and vomiting	3-4[c]	Hold	Hold	Toxicity resolves to ≤Grade 2[a]	Resume at 100%
	All Other Non-Hematologic Toxicities[a,f,i]	3-4[c]	Hold	Hold	Toxicity resolves to ≤Grade 2[a]	Follow standard of care guidelines

Abbreviations: AE=adverse event; G-CSF=granulocyte colony-stimulating factor; Gem=gemcitabine; Cis=cisplatin; N/A=not applicable

a. Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
b. See the package insert of each of the G-CSF drugs for administration of G-CSF for neutropenia.
c. Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after a Grade 4 drug-related AE.
d. Permanently discontinue gemcitabine and cisplatin if gemcitabine-/cisplatin-related hematologic toxicity does not resolve to ≤Grade 2 within 6 weeks.
e. If Day 8 study intervention is delayed by ≥2 weeks, then subsequent therapy should start with next cycle. Pembrolizumab should be given on Day 1 of each new cycle. There should be at minimum a 3-week interval between pembrolizumab doses and a minimum 1-week interval between the chemotherapy doses.
f. Gemcitabine should be administered with caution in participants with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.
g. Follow local cisplatin product label recommendations if dosing considerations are more stringent.
h. Administration may be interrupted or reduced at the discretion of the investigator.
i. Allow continuous treatment for laboratory AEs that are asymptomatic and deemed to be not clinically significant.

Other Allowed Dose Interruption for Gemcitabine or Cisplatin

Gemcitabine or cisplatin may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 6 weeks of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.1.3 Guidance for Management of Hepatic Events of Clinical Interest

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

For dose interval modification, refer to Sections 6.6.1.1 and 6.6.1.2.

ALT:

- Among participants with Baseline ALT <2×ULN: ALT ≥5×ULN
- Among participants with Baseline ALT ≥2×ULN: ALT >3× the Baseline level
- ALT >500 U/L regardless of baseline level

Total bilirubin:

- Total bilirubin >3.0 mg/dL

Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:

- New onset clinically detectable ascites requiring intervention for >3 days
- Hepatic encephalopathy
- Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)

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

Immediate assessment in case of HECI:

All Participants

All participants should be considered for evaluation according to the directions below within 72 hours of the alert for a nonoverdose ECI. Laboratory assessments of HECIs will be performed locally; central laboratory is acceptable if local laboratory is not available.

Procedures:

- Consider obtaining a consultation with a hepatologist
- Obtain a workup for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus
- Assess for ingestion of drugs/supplements with hepatotoxic potential
- Assess for alcohol ingestion
- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Repeat ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, γ glutamyl transpeptidase, INR, and complete blood count with differential
- Measure HCV RNA viral load (applies only for participants who have current active HCV infection or had infection in the past)
- HBV DNA, HBsAg, anti-HBc (total and IgM), and anti-HBs regardless of prior HBV status (Note: participants should be questioned about compliance with the use of antiviral agents)
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated

BTC 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. CCI [redacted] CCI [redacted] CCI [redacted] The following section provides further guidance on the diagnosis and management of potential hepatic complications among BTC participants in this study. The recommendation is to hold study interventions for 1 to 2 days. If toxicity does not improve within 1 to 2 days or worsens, follow “Management of HECI” below.

Table 8 Management of HECI for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

If HECI is determined to be due to other causes, cisplatin can be restarted if infection is ruled out and otherwise deemed clinically appropriate by the investigator.

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

	Diagnosis	Management
Immune-related hepatitis	If any of the HECI criteria is met as defined in the protocol Section 8.4.7 Note: Immune-related hepatitis is a diagnosis made after excluding other possible etiologies such as viral flare, biliary or vascular obstruction, infection, medications, and alcohol use usually immune-related hepatitis response to dechallenge and/or steroids and reoccurs with rechallenge	Interrupt 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, total bilirubin, direct bilirubin, ALP, and INR. **Restart study 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 study intervention if:** a. Laboratory abnormalities do not resolve within 3 weeks
Other Causes	Rule out infection with blood, urine, and ascites culture – antibiotics should be started if infection is found If total bilirubin is elevated, imaging should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression by imaging Rule out alcohol use and hepatotoxic drugs including herbal and alternative medications	Restart study intervention only if laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade **within 6 weeks.** If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.

ALP=alkaline phosphatase; anti-HBs=hepatitis B surface antigen antibody; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CP-C=Child-Pugh Grade C; DNA=deoxyribonucleic acid; ECI=event of clinical interest; HBV=hepatitis B virus; HCV=hepatitis C virus; HECI=hepatic events of clinical interest; INR=international normalized ratio; IV=intravenous; RNA=ribonucleic acid; TND=target not detected; ULN=upper limit of normal.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is blinded but 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 (refer to Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic IRT should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 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
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.2.1 require sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention
- The participant has a confirmed positive serum pregnancy test

- Participant has any of the following nonoverdose hepatic ECIs:
  - ALT >20×ULN (confirmed within 1 week)
  - Drug-related total bilirubin >10 x ULN
  - CPS of >9 points
- Unacceptable toxicity, as described in Section 6.6

  Note: Participants who discontinue one or all components of chemotherapy due to toxicity or AEs can continue with pembrolizumab or placebo up to the full 35 administrations
- Prohibited concomitant medication requiring discontinuation of study intervention (refer to Section 6.5)
- Radiographic disease progression outlined in Section 8.2.1.5 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond iCRO-verified disease progression)
- Any progression or recurrence of any malignancy, or occurrence of another malignancy, that requires active treatment
- Discontinuation of pembrolizumab/placebo for recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above (refer to Section 6.6.1.1), that are presumed to be immune-related

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

7.2 Participant Withdrawal From the Study

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

As clinical event data are important study endpoints, participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue all remaining study visits for follow-up and vital status assessment as outlined in the SoA and Section 8.11.3.

The investigator is to inform the participants that:

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

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

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

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

Participants who withdraw consent during the study

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

Section 8.1.9 delineates the specific procedures performed at the time of withdrawal and withdrawal from future biomedical research. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (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 future biomedical research. If there is a change to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The

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

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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

The 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 future biomedical research consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The investigator/designee will collect all active conditions and any condition diagnosed within

the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before C1D1. 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. In addition, new medications started during the Second Course through the Second Course Safety Follow-up visit should be recorded.

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 randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Administration of study intervention will be monitored by the investigator and/or study staff and/or qualified designee per institutional guidelines and procedures.

Study intervention should begin within 3 days of randomization.

8.1.8.1 Timing of Dose Administration

Study intervention should be administered after all procedures/assessments have been completed. Study intervention may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for C1D1, where the acceptable window is +3 days from randomization. Pembrolizumab or placebo infusion will be administered first, and then administration of chemotherapy, according to local guidelines and practices.

8.1.8.1.1 Pembrolizumab

Pembrolizumab 200 mg or placebo will be administered as a 30-minute IV infusion, every 3 weeks. 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).

Every effort should be made to begin the first dose of study intervention on the day of randomization, but if this is not achieved, study intervention should be initiated no later than 3 days from the date of randomization.

All subsequent pembrolizumab or placebo cycles may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment.

The Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

8.1.8.1.2 Gemcitabine/Cisplatin

Cisplatin will be administered as an IV infusion on Day 1 and Day 8 of a 3-week cycle and should be immediately preceded and followed by hydration procedures and administered according to local guidelines/product label procedures. Cisplatin may be administered on Day 2, if required per local guidelines; however, Day 1 is the preferred day for intervention administration. Gemcitabine will be administered as an IV infusion on Days 1 and 8 of a 3-week cycle, according to local guidelines and product label procedures.

Premedication with antiemetic therapy can be given prior to cisplatin and gemcitabine administration. Consider following Multinational Association of Supportive Care in Cancer (MASCC) guidelines (http://www.mascc.org/antiemetic-guidelines) and, including a 5-HT3 receptor antagonist, dexamethasone (or equivalent) and aprepitant (or equivalent) as per the

MASCC guidelines. Based on data showing potential impact of steroid use on efficacy of PD-1 and PD-L1 blockade, systemic steroid use as anti-nausea medication should be limited as deemed safe by the investigator [Arbour, K. C., et al 2018].

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the study intervention period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

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

8.1.9.1 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 by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant’s intervention assignment, the

investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

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

For studies that require nonemergency unblinding as part of the study design (eg, disease progression) to support treatment decisions, IRT should be used to unblind the participant's treatment assignment. The emergency unblinding center should not be used for this purpose.

Once an emergency unblinding or a nonemergency 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.

Treatment identification information is to be unblinded ONLY in the following situation:

1. For the welfare of the participant, if necessary.

2. Participants requiring second course who completed 35 cycles and stopped first course study intervention with SD or better including CR and had to discontinue for any reason other than disease progression or intolerability. Such participants must have experienced radiographic disease progression while off study intervention according to the criteria in Section 6.1.2.

Note: PD-L1 status will remain blinded to the participant and the investigator.

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

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

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.

8.1.12 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required and is to be:

- A newly obtained core or incisional biopsy of a tumor lesion, which was not previously irradiated

or

- An archival tumor tissue sample if a new biopsy is unavailable (depending on protocol requirements)

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Details pertaining to tumor tissue submission can be found in the Procedures Manual.

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only [IUO]) diagnostic kit. The diagnostic test is identical to the US FDA approved PD-L1 IHC 22C3 pharmDx kit except it is labeled IUO.

The PD-L1 result will be masked to the site.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the iCRO can be found in the Site Imaging Manual (SIM).

Tumor imaging by CT/MRI chest, abdomen and pelvis is required at all scheduled imaging time points (CT is strongly preferred). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice.

Whole body radionuclide bone scan is as clinically indicated at baseline and on study. MRI/CT (MRI is strongly preferred) brain imaging is only as clinically indicated at baseline and on study.

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.

Participant eligibility will be determined using local assessment (investigator assessment) based on RECIST 1.1. All scheduled images for all study participants from the sites will be submitted to the iCRO. In addition, images (including via other modalities) that are obtained

at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which shows radiologic progression, should also be submitted to the iCRO.

When the investigator identifies radiographic progression per RECIST 1.1, the iCRO will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor via email (refer to Section 8.2.1.5 and Figure 2). Treatment should continue until PD has been verified by BICR (if initial site-assessed PD was not verified by BICR, each subsequent scan must be submitted to iCRO with verification of PD request until PD has been verified by BICR). Regardless of whether PD is verified, if the investigator considers the participant has progressed, but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the iCRO.

8.2.1.1 Initial Tumor Imaging

The screening images must be submitted to the iCRO for retrospective review.

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

Tumor imaging at baseline includes the following:

- CT/MRI of the chest, abdomen, and pelvis
- MRI/CT of the brain when clinically indicated
- Bone scan whole body when clinically indicated

8.2.1.2 Tumor Imaging During the Study

On study first scheduled imaging assessment must be performed 6 weeks (42 days +7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) through Week 54. Participants who remain on treatment beyond Week 54 will have imaging performed every 12 weeks (84 days ±7 days).

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

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for

confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the BICR.

Per iRECIST (Section 8.2.1.6), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 8.2.1.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study intervention. Exceptions are detailed in Section 8.2.1.6.

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

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

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment calculated from the date of randomization (refer to Section 8.2.1.2).

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

- disease progression as defined by RECIST 1.1 verified by BICR
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

Participants who are clinically stable and treated past radiographic progression may continue to be assessed until progression is confirmed according to the rules of iRECIST, when clinically appropriate.

8.2.1.4 Second Course (Retreatment) Tumor Imaging

Tumor scans must be performed within 28 days before restarting study intervention with pembrolizumab.

If disease progression has been verified by BICR for the First Course, the Second Course may be initiated. The disease progression scan may be used as the Second Course baseline scan if performed within 4 weeks prior to dosing and meets scan standards.

The first scan should be performed at 6 weeks (42 days +7 days) after restarting study intervention. Subsequent tumor scans are to be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

Scans should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, completion of Second Course, or notification by the Sponsor, whichever occurs first.

If participants discontinue study intervention, tumor scans are to be performed at discontinuation (±4 week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans every 12 weeks (84 days ±7 days) until the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

The only Second Course scan to be provided to the iCRO is the baseline scan if it is the final scan for the Initial Treatment or First Course.

8.2.1.5 RECIST 1.1 Assessment of Disease

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

Upon investigator-assessed disease progression, the indicative scans are to be submitted immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
    - resume imaging per protocol schedule (≥4 weeks to next scan)

  - send scans to iCRO
  - continue local assessment
  - do not change investigator assessment of progression
  - if subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification

- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anti-cancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

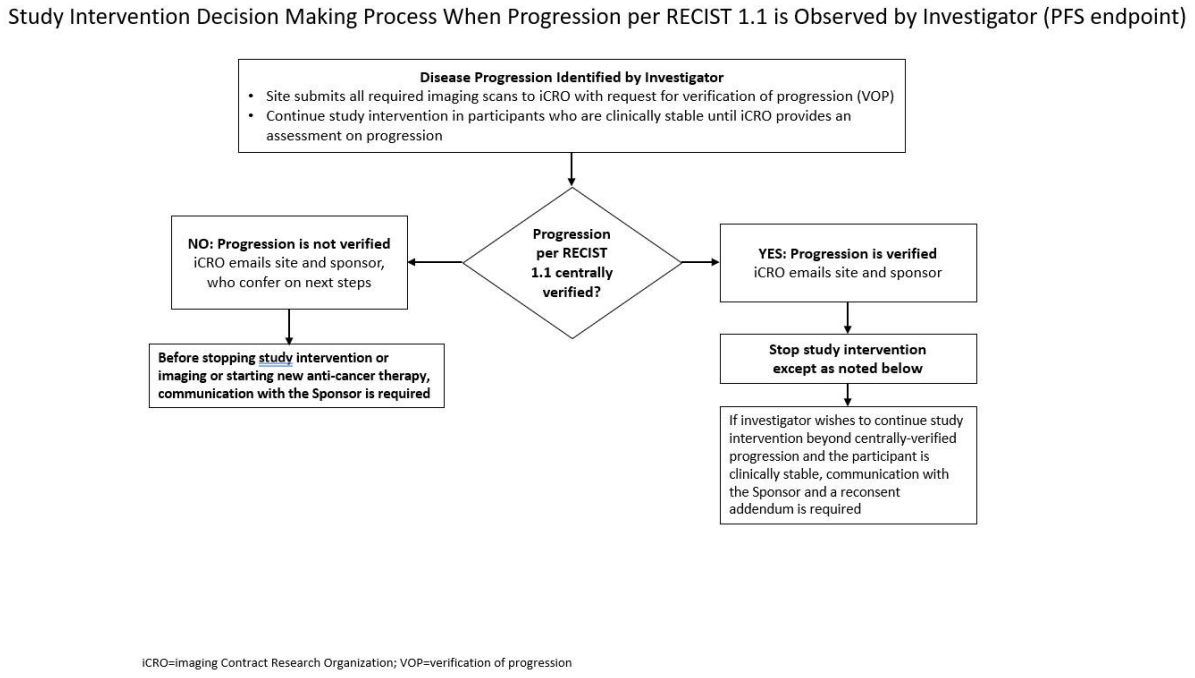
If disease progression is verified, the process continues as follows:

- investigator judgement will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the sponsor is required and a reconsent addendum must be signed
- obtain scans locally per original protocol schedule
- do not send scans to iCRO

Figure 2 illustrates the study intervention decision process involving verification of disease progression for participants.

- For the purpose of this decision process, lack of clinical stability is defined as:
  - unacceptable toxicity
  - clinical signs or symptoms indicating clinically significant disease progression
  - decline in performance status
  - rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

Figure 2 Study Intervention Decision Making Process When Progression per RECIST 1.1 is Observed by the Investigator (PFS Endpoint)



8.2.1.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions [Seymour, L., et al 2017]. When clinically stable, participants may continue study intervention beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in Appendix 8. iRECIST reflects that some participants can have a transient tumor flare after the start of immunotherapy then experience subsequent disease response. This data will be captured in the clinical database.

- If the participant is clinically stable (refer to Sec. 8.2.1.5), continue study intervention per protocol
  - Perform scans 4 to 8 weeks after RECIST 1.1 progression
  - Continue investigator assessment per iRECIST
  - If progression is BICR-verified, stop sending scans to iCRO
  - If the participant is not clinically stable, best medical practice is to be applied.

8.2.2 Patient-reported Outcomes

The EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-BIL21 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EQ-5D-5L first, then EORTC QLQ-C30, then EORTC QLQ-BIL21. See the SoA (Section 1.3.1) for ePRO administration schedule.

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

If at the time of enrollment of a participant, the translated version of the EQ-5D-5L, EORTC QLQ-C30 and/or EORTC QLQ-BIL21 questionnaires are not available for that language/country, and therefore cannot be completed by the participant at Cycle 1 Day 1, then the EORTC QLQ-C30 and/or EORTC QLQ-BIL21 will not be required for this participant at any point during the study. The other study PRO measures must be completed as scheduled.

NOTE: For some sites, the translated EORTC QLQ-C30 and/or EORTC QLQ-BIL21 might become available after study start-up and should be administered to participants at their time of enrollment; for some sites, the EORTC QLQ-C30 and/or EORTC QLQ-BIL21 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 below.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period and at the time of study intervention discontinuation. Clinically significant abnormal findings should be recorded as medical history. 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 including signs of liver decompensation (eg, hepatic encephalopathy and ascites).

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination, as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination, including

special attention to signs of liver decompensation (eg, hepatic encephalopathy and ascites), as clinically indicated, prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Day 8 directed physical examination will not be performed when both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

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

8.3.2 Audiometry

Participants receiving cisplatin should be monitored for audiological complications. Audiometry testing will be performed at Screening or per local standard, by the investigator or medically qualified designee (consistent with local requirements). Assessments may be repeated during the study, as clinically indicated. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.3 Vital Signs

The investigator or qualified designee will take vital signs at Screening, prior to the administration of each dose of study intervention, at study discontinuation, and during the Follow-up Period, as specified in the SoA (Section 1.3). Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at the screening visit only.

Day 8 vital signs will not be assessed/performed when both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

8.3.4 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed using local standard procedures once at Screening. Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

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 Intervention), 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.

Day 8 hematology, chemistry and liver panel blood samples will not be collected after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

Repeat HBV viral load and HBsAg testing approximately every 6 weeks if HBsAg negative and anti-HBc positive and HBV viral load is undetectable at screening and not on antiviral therapy and approximately every 12 weeks for participants on antiviral therapy for HBV until the end of study intervention and then per local standard of care. This testing should be aligned with study intervention visits.

8.3.5.2 Pregnancy Testing

- Pregnancy testing:

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

  - Pregnancy testing (urine or serum as required by local regulations) should be conducted every 3 weeks during the Study Intervention Phase.

  - Pregnancy testing (urine or serum as required by local regulations) should be conducted approximately 240 days after the last dose of chemotherapy or 150 days after the last dose of pembrolizumab or placebo, whichever is greater, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy.

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

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

8.3.6 Performance Assessments

8.3.6.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with Grades 0 to 5.

The investigator or qualified designee will assess ECOG status (see Appendix 9) at Screening, prior to the administration of each dose of study intervention and during the Follow-up Period, as specified in the SoA (Section 1.3). If ECOG status assessment is performed prior to dosing on C1D1, then Screening ECOG is not mandatory.

Day 8 ECOG status will not be performed after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.

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

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators 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 randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes 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 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 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 the time required to eliminate systemic exposure after cessation of study intervention as described in [Sections 5.1 and 8.3.5], or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 9.

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

Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth

must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

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

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

The Sponsor (via the external data monitoring committee [eDMC]) will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the 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:

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

b. **Hepatic ECIs as defined in Section 6.6.1.3.** For guidance related to the diagnosis and management of hepatic ECIs, refer to Section 6.6.1.3.

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.

An overdose for gemcitabine or cisplatin will be defined as any dose exceeding the prescribed dose by 20%.

Treatment of overdose of gemcitabine or cisplatin should follow the guidelines in the relevant product labels. 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

The decision as to which blood samples collected will be assayed for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of antidrug antibodies (ADA) and PK are currently planned as shown in the SoA (Section 1.3.1). Blood samples will be obtained to measure PK of serum pembrolizumab. The pembrolizumab serum maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times will be summarized. If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab clinical studies, it may be decided to discontinue or reduce further sample collection in this study.

8.6.1 Blood Collection for PK for MK-3475

Sample collection, storage, and shipment instructions for serum samples will be provided in the laboratory manual. Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants in the SoA (Section 1.3.1).

8.6.2 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the laboratory manual. Anti-pembrolizumab antibody samples should be drawn according to the ADA collection schedule for all participants in the SoA (Section 1.3.1). Simultaneous PK sampling is required for interpretation of ADA analysis.

8.6.3 Blood Collection for RNA Analyses and Plasma and Serum Biomarker Analyses

Blood should be collected predose for C1D1, C2D1, C5D1, and at End of Intervention (EOI). CCI [redacted] will be stored at the end of the study for future biomedical research if the participant has consented (refer to Section 8.9).

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]

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

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

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn CCI [redacted] CCI [redacted] This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, CCI [redacted] will be stored for future biomedical research if the participant provides documented informed consent for future biomedical research. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

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

8.8.2 Tissue Sample

All participants must submit either a newly obtained core or excisional biopsy or archival tissue (fine needle aspirate is not adequate for both archival and new tissue samples) to a central vendor for characterization of biomarker evaluation and deemed adequate for evaluation prior to randomization. Submission of formalin-fixed, paraffin-embedded block specimens are preferred to slides. If the sample is determined to be nonevaluable prior to

testing by the central laboratory, a new sample must be submitted and deemed adequate by the central vendor prior to participant randomization. Detailed instructions for tissue collection, processing, and shipment are provided in the laboratory manual.

If the participant provides documented informed consent for future biomedical research, any leftover samples that would be ordinarily discarded at the end of the main study will be retained for future biomedical research.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- Leftover specimens listed in Section 8.8 Biomarkers.

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

All-cause hospitalizations and emergency department visits must be reported in the eCRF, from the time of study 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.

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 provided 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 14 days prior to the first dose of study intervention. An exception is hepatitis testing which may be performed up to 28 days prior to the first dose of study intervention. Evaluation of ECOG is to be performed within 3 days prior to the first dose of study intervention.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours (urine) or 72 hours (serum) prior to the first dose of study

intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Tumor tissue from a fresh core or excisional biopsy or archival is acceptable. Archival tissue must be <5 years of age from the time of sample submission.

8.11.1.1 Rescreening

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. For repeat hepatitis 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 the Sponsor. Participants may not rescreen more than 1 time without consulting with the Sponsor. Participants who are rescreened will retain their original screening number.

8.11.2 Study Intervention Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1 through 8.11.

8.11.3 Post-intervention Visit

8.11.3.1 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.

Participants who are eligible for retreatment with pembrolizumab may have up to 2 safety follow-up visits: 1 after the Initial Treatment or First Course and 1 after the Second Course.

8.11.3.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up and should be assessed Q6W (42 days ±7 days) through Week 54 and Q12W (84 days ±7 days) thereafter to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study, or if the participant begins retreatment. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

Participants who complete all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6 will move from Efficacy Follow-up to Second Course when they experience disease progression. Details are provided in the SoA (Section 1.3).

8.11.3.3 Survival Follow-up Assessments

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

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

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

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

8.11.4 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.

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 E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the clinical study report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data or PROs) will be documented in a sSAP or separate analysis plans.

Details pertaining to the statistical analyses for participants enrolled in China will be provided in a separate sSAP.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3 Randomized, Double Blind Study of Pembrolizumab Plus Gemcitabine/Cisplatin versus Placebo Plus Gemcitabine/Cisplatin as First-Line Therapy in Participants with Advanced and/or Unresectable Biliary Tract Carcinoma
Study Intervention Assignment	Participants will be randomized in a 1:1 ratio to receive pembrolizumab plus gemcitabine/cisplatin (experimental arm) or placebo plus gemcitabine/cisplatin (control arm). This is a double-blind study. Study Intervention allocation/randomization will be stratified according to the following factors: • Geographic region (Region 1: Asia versus Region 2: Non-Asia) • Locally advanced versus metastatic • Site of Origin (gallbladder/intrahepatic/extrahepatic)
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoint/Hypothesis	Overall survival (OS)
Statistical Methods for Key Efficacy Analyses	The primary and secondary hypotheses will be evaluated by comparing pembrolizumab plus gemcitabine/cisplatin to placebo plus gemcitabine/cisplatin in OS and PFS using stratified log-rank tests. Estimation of the HR will be performed using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with strata weighted by sample size will be used for analysis of ORR.
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.

Interim Analyses	Two interim analyses are planned in this study. Results will be reviewed by an external data monitoring committee. Details are provided in Section 9.7.
	• Interim Analysis 1 (IA1)
	  ○ Timing: To be performed when ~585 OS events have been observed and ~26 months passed since the start of randomization.
	  ○ Primary purpose: Interim analysis for OS and final analyses for PFS and ORR.
	• Interim Analysis 2 (IA2)
	  ○ Timing: To be performed when ~695 OS events have been observed and ~32 months passed since the start of randomization.
	  ○ Primary purpose: Interim analysis for OS.
	• Final Analysis
	  ○ Timing: To be performed when ~818 OS events have been observed and ~38 months passed since the start of randomization
	  ○ Primary purpose: Final analysis for OS

Multiplicity	The overall Type I error over the primary and secondary hypotheses is strongly controlled at 2.5% (1-sided), with 2.5% initially allocated to OS (H1). By using the graphical approach of Mauer and Bretz [Maurer, W., et al 2011], if one null hypothesis is rejected, the alpha will be shifted to other hypotheses. The alpha value will be passed for testing PFS and ORR if the OS null hypothesis is rejected.
Sample Size and Power	The planned sample size was 1048 participants, but the updated power calculations are based on 1069 participants, which is the actual final number of randomized participants. It is estimated that there will be ~818 deaths at the OS final analysis. With 818 deaths, the study has ~93% power to reject the null OS hypothesis under the alternative hypothesis (HR=1 for the first 2 months from randomization followed by HR=0.75 after 2 months) at an initially assigned 2.5% (1-sided) significance level.
China Extension (if applicable)	China participants randomized during the global portion will be included in all global portion analyses (efficacy and safety). China participants randomized during the China extension portion will be excluded from all global portion analyses. China participants randomized during global and extension portion will both be included in the China-specific analyses.

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.

The investigator and Sponsor study team (clinical, statistical, statistical programming and data management personnel) will be blinded to participant level PD-L1 biomarker results. PD-L1 biomarker results will not be shared with the site staff or participants. An unblinded Sponsor clinical scientist, statistician, and statistical programmer will have access to participant level PD-L1 results for the purpose of data review and will have no other responsibilities associated with the study. A summary of PD-L1 biomarker prevalence may be provided to the Sponsor study team by the unblinded designated Sponsor statistician. Further documentation will be provided in the sSAP. In addition, imaging will be performed by BICR without knowledge of treatment assignments or PD-L1 status.

Blinding procedures related to the planned IAs are described in Section 9.7. Blinding to treatment will be maintained at all investigational sites. Analyses or summaries generated by randomized treatment assignment or actual treatment received at the planned IAs will be provided by the external unblinded statistician to the DMC.

Extension Study in China (if applicable)

For all participants in China, including participants randomized in the global portion and the extension portion, participant level treatment information will be blinded to the statistician(s)/programmer(s) responsible for the China extension portion analysis until the extension portion database lock is achieved. The extent to which individuals are unblinded to the results will be limited. Blinded and unblinded individuals will be clearly documented.

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

- **Overall Survival (OS)**

  OS is defined as the time from randomization to death due to any cause.

Secondary

- **Progression-free survival (PFS)**

  PFS is defined as the time from randomization to the first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first.

- **Objective Response Rate (ORR)**

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

- **Duration of Response (DOR)**

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

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, fatal AEs, laboratory tests, and vital signs. Furthermore, specific events will be collected and designated as ECIs, as described in Section 8.4.7.

9.4.3 Patient-Reported Outcome Endpoints

The following exploratory PRO endpoints will be evaluated, as described in Section 3:

- Change in patient-reported outcomes from baseline in EORTC QLQ-C30 and EORTC QLQ- BIL21 global health status/QOL score

- Time to deterioration (TTD) in EORTC QLQ-C30 and EORTC QLQ-BIL21 global health status/QOL score

TTD is defined as the time from baseline to the first onset of PRO deterioration. PRO deterioration is defined as a PRO score decrease of 10 points or more (out of 100), with subsequent confirmation [Osoba, D., et al 1998]. Details will be provided in the sSAP.

9.5 Analysis Populations

Extension Portion of the Study in China (if applicable)

After the sample size required for the global portion is reached, the study may continue to randomize participants in China alone until the sample size for China participants reaches the target number of participants. The China participants randomized after the enrollment of the global portion is closed will not be included in the global portion primary analysis population. The ITT participants in China, including all participants in China randomized in the global portion and the extension portion, will be analyzed for China-specific analysis.

9.5.1 Efficacy Analysis Populations

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

based on the population of responders (participants that achieved complete or partial response). The reasons for exclusion from the ITT population (if any) will be summarized.

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 intervention period; such participants will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives the incorrect study medication for 1 cycle, but receives the correct study intervention for all other cycles, will be analyzed according to the correct treatment group, and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study 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 analyses of PRO endpoints will be based on a quality of life-related full analysis set (FAS) population following ICH E9 guidelines. This population consists of all randomized participants who have received at least 1 dose of study intervention and have completed at least 1 PRO assessment for the specific endpoint. Participants will be analyzed in the treatment group to which they are randomized.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary efficacy objectives. Methods related to exploratory objectives will be described in the sSAP. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity. The 3 stratification factors used for randomization; geographic region (Region 1: Asia versus Region 2: Non-Asia), locally advanced versus metastatic, and site of origin (gallbladder/intrahepatic/extrahepatic) will be applied to all stratified efficacy analyses (in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]). The analysis stratification will be based on the value of the randomization factor entered into the IVRS. If required, some of the small strata among the 12 strata formed by the 3 factors might be pooled for analyses; the pooling strategy will be documented in the sSAP prior to the database lock for the first

interim analysis. Decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

The efficacy analyses for ORR, DOR and PFS will include responses and documented progression events that occur before the Second Course treatment.

9.6.1.1 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The hypotheses of treatment difference in survival will be tested by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. With a piecewise constant HR (as is the case with the delayed effect working model), the HR estimate from the Cox model is approximately equal on the log scale to the average of the HRs in each period weighted proportionally to the number of events in the period. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact.

9.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment arm. The hypotheses of treatment difference in PFS will be tested by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment effect (ie, HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Additional analyses will be performed for comparison of PFS based on investigator's assessment.

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

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention to treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers discontinuation of study intervention due to reasons other than complete response or initiation of new anticancer treatment, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analyses are summarized in Table 10.

Table 10 Censoring Rules for Primary and Sensitivity Analyses of PFS

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

Abbreviations: PD=progressive disease; PFS=progression-free survival.

9.6.1.3 Objective Response Rate

The Stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with weights proportional to the stratum size will be used for comparison of the ORRs between the treatment arms. The same stratification factors used for randomization (Section 6.3.2) will be used as stratification factors in the analysis. A 95% CI for the difference in response rates between the treatment arms will be provided. Additional supportive unstratified analyses may also be provided. An additional analysis will be performed for the comparison of ORR based on the investigator's assessment.

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

9.6.1.4 Duration of Response

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed CR or PR will be included in this analysis.

Censoring rules for DOR are summarized in Table 11. For the DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 11 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. Abbreviations: DOR=duration of response; PD=progressive disease.		

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 12.

Table 12 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date or data cutoff date, whichever is the earliest
Key Secondary Analyses			
PFS per RECIST 1.1 by BICR	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 10
ORR per RECIST 1.1 by BICR	Testing and estimation: stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]	ITT	Participants with missing response data are considered non-responders.
Abbreviations: BICR=blinded independent central review; ITT=intention to treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.			

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

9.6.2 Statistical Methods for Safety Analyses

The primary safety analyses will include only events that occur before the Second Course Treatment. Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs and laboratory tests.

The analysis of safety results will follow a tiered approach (Table 13). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) are either prespecified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

AEs that are immune mediated or potentially immune mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Similarly, the combination of pembrolizumab and gemcitabine/cisplatin has not been associated with any new safety signals. Therefore, there are no Tier 1 events defined for this study.

Tier 2 Events

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

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other adverse experiences will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 event because the population enrolled in this study are in critical conditions and usually experience various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AE (≥5% of participants in one of the treatment groups) and SAE (≥5% of participants in one of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

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

Continuous Safety Measures

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

Table 13 Analysis Strategy for Safety Parameters

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

9.6.3 Statistical Methods for Patient-reported Outcome Analyses

To evaluate the treatment effect on the health-related QOL outcomes at prespecified time points (provided in the sSAP), a constrained longitudinal data analysis (cLDA) model will be applied, with the PRO score as the response variable, and the treatment by time interaction and stratification factors as covariates. Least square mean (LS mean) change from baseline will be summarized. Groupwise comparisons will be performed and model-based LS mean score will be provided by treatment group and study visit.

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

Time to deterioration is defined as the time from the baseline PRO assessment to deterioration or death, whichever occurs first [Yang, J. C., et al 2013]. The Kaplan-Meier method will be used to estimate times to deterioration survival curve for each treatment arm. Stratification factors used for allocation will be used in the stratified Cox proportional hazards models. The HR, 95% CI, and nominal p-value will be reported.

Details of PRO analyses will be described in the sSAP.

9.6.4 Statistical Methods for Pharmacokinetics (PK) Analyses

Plasma concentration versus time data will be pooled with data from existing studies and will be analyzed using a population PK approach to estimate population PK parameters. The detailed methods will be included in a separate analysis plan prior to the planned first interim efficacy analysis.

9.6.5 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized and the primary reason for discontinuation will be displayed. Demographic variables (such as age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

9.7.1 Efficacy 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 EOC (refer to Section 10.1.4.2) of the Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the

study, the EOC and limited additional Sponsor personnel may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details will be provided in the eDMC Charter.

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

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 14.

Table 14 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Primary Purpose of Analysis
IA1	OS	~585 OS events have been observed and ~26 months passed since the start of randomization.	• Interim OS analysis • Final PFS and ORR analyses if OS superiority is established
IA2	OS	~695 OS events have been observed and ~32 months passed since the start of randomization.	• Interim OS analysis
FA	OS	~818 OS events have been observed and ~38 months passed since the start of randomization.	• Final OS analysis
Abbreviations: FA=final analysis; IA1=interim analysis 1; IA2=interim analysis 2; OS=overall survival.			

9.7.2 Safety Interim Analyses

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

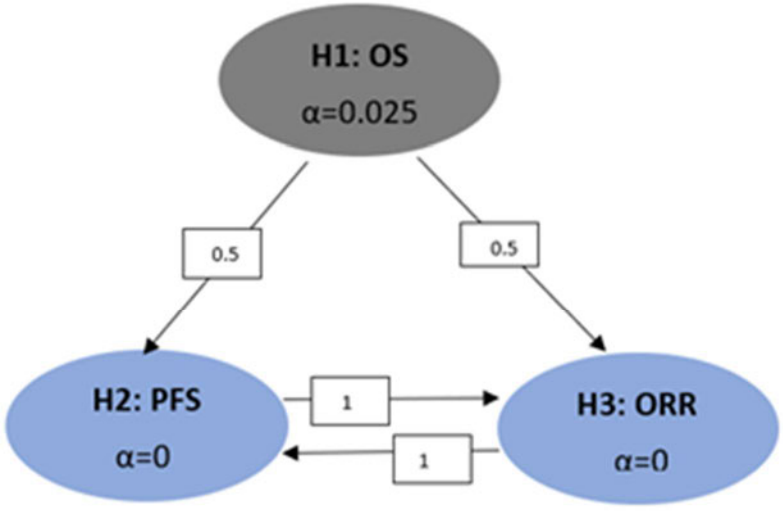
9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W., et al 2011] to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypotheses. Figure 3 shows the initial one-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

The initial α assigned to OS will be 0.025. If OS hypothesis is rejected, the corresponding alpha will be reallocated equally to PFS and ORR. If the PFS hypothesis is rejected, the corresponding alpha will be reallocated to ORR. If the ORR hypothesis is rejected, the corresponding alpha will be reallocated to PFS.

Within each endpoint, the Type I error control across the interim and final analyses will be maintained by the use of the Lan-DeMets spending function approach with O'Brien-Fleming boundaries.

Figure 3 Multiplicity Diagram for Type I Error Control



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

9.8.1 Overall Survival

The initial α-level for testing OS is 0.025. Under the alternative hypothesis, the treatment effect will be delayed by 2 months, with OS HR=1 in the first 2 months, and HR=0.75 after 2 months. CCI
CCI

CCI

[redacted]

CCI

[redacted]

CCI [redacted] At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an interim analysis and leave reasonable alpha for the FA, the minimum alpha spending strategy will be adopted. At an IA, the information fraction used in Lan-DeMets spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically,

- In the scenario that the events accrue slower than expected and the observed number of events is less than the expected number of events at a given analysis, the information fraction will be calculated as the observed number of events at the IA over the target number of events at FA.

- In the scenario that the events accrue faster than expected and the observed number of events exceeds the expected number of events at a given analysis, then the information

fraction will be calculated as the expected number of events at the IA over the target number of events at FA.

The FA will use the remaining Type I error that has not been spent at the earlier analyses. The event counts for all analyses will be used to compute the correlations.

Of note, while the information fraction used for alpha spending calculation will be the minimum of the actual information fraction and the expected information fraction, the correlations required for deriving the bounds will still be computed using the actual information fraction based on the observed number of events at each analysis over the target number of events at the FA.

The minimum spending approach assumes timing is not based on any observed Z-value and thus the Z test statistics used for testing conditioned on timing are multivariate normal. Given the probabilities derived with the proposed spending method, the correlations based on actual event counts are used to compute bounds that control the Type I error at the specified alpha level for a given hypothesis conditioned on the IA timing. Since this is true regardless of what is conditioned on, the overall Type I error for a given hypothesis unconditionally is controlled at the specified level. By using more conservative spending early in the study, power can be retained to detect situations where the treatment effect may be delayed.

9.8.2 Progression-free Survival

The PFS hypothesis is not allocated any α initially and can only be tested when the OS is successful. The study will test PFS at IA1 (final PFS analysis). The p-value based on PFS data observed at IA1 will be calculated and compared to its corresponding p-value bound when OS demonstrates superiority and α for PFS test becomes available (which might happen at OS IA1, IA2 or FA). A descriptive analysis of PFS may also be provided at the IA2 or FA data cutoff when superiority in OS is demonstrated.

Following the multiplicity strategy as outlined in Figure 3, the PFS hypothesis may be tested at α=0.0125 (if the OS null hypothesis is rejected), or at α=0.025 (if both the OS and ORR null hypotheses are rejected). Under the alternative, the treatment effect will be delayed by 2 months, with PFS HR=1 in the first 2 months, and HR=0.7 after 2 months. Table 16 shows the boundary properties and power for each of these α levels for the PFS analysis.

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

Analysis	**Value**	**α = 0.0125**	**α = 0.025**
IA1 (Final PFS analysis)	Z	2.2414	1.9600
N: 1069	p (1-sided)[a]	0.0125	0.0250
Events: 786	HR at bound[b]	0.8554	0.8695
Month: ~26	P(Cross) if HR = 1[c]	0.0125	0.0250
	P(Cross) under the alternative hypothesis[d,e]	0.9176	0.9518

Abbreviations: HR=hazard ratio; IA1=interim analysis 1; PFS=progression-free survival.
The number of events is estimated.
[a] The nominal α for testing.
[b] The approximate HR required to reach an efficacy bound.
[c] P(Cross if HR = 1) is the probability of crossing a bound under the null hypothesis.
[d] The alternative hypothesis is HR=1 for the first 2 months and HR=0.7 after 2 months.
[e] P(Cross) under the alternative hypothesis is the probability of crossing a bound under the alternative hypothesis.

9.8.3 Objective Response

The ORR hypothesis is not allocated any α initially and can only be tested when the OS is successful. The study will test ORR at IA1 (final ORR analysis). The p-value based on ORR data observed at IA1 will be calculated and compared to its corresponding p-value bound when OS demonstrates superiority and α for ORR test becomes available (which might happen at OS IA1, IA2 or FA). A descriptive analysis of ORR may also be provided at the IA2 or FA data cutoff when superiority in OS is demonstrated.

Table 17 shows the boundary properties for 2 possible 1-sided α-levels as well as the approximate treatment difference required to reach the boundary (ORR difference) which were derived using a Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for ORR.

Table 17 Efficacy Boundaries and Properties for Objective Response Analyses

Analysis	Value	α level=0.0125	α level=0.025
IA1 N: 1069	Z	2.2414	1.9600
	p (1-sided) [a]	0.0125	0.0250
	delta at bound [b]	0.0627	0.0548
	P(Cross) if delta=0 [c]	0.0125	0.0250
	P(Cross) if delta=0.1 [d]	0.9088	0.9470

Abbreviations: IA1=interim analysis 1; ORR=objective response rate.

[a] The nominal α for testing.

[b] Delta at bound is the approximate delta required to reach an efficacy bound.

[c] P(Cross if delta=0) is the probability of crossing a bound under the null hypothesis, with an underlying ORR of 25% in both treatment groups.

[d] P(Cross if delta=0.1) is the probability of crossing a bound under the alternative hypothesis.

9.8.4 Safety Analyses

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

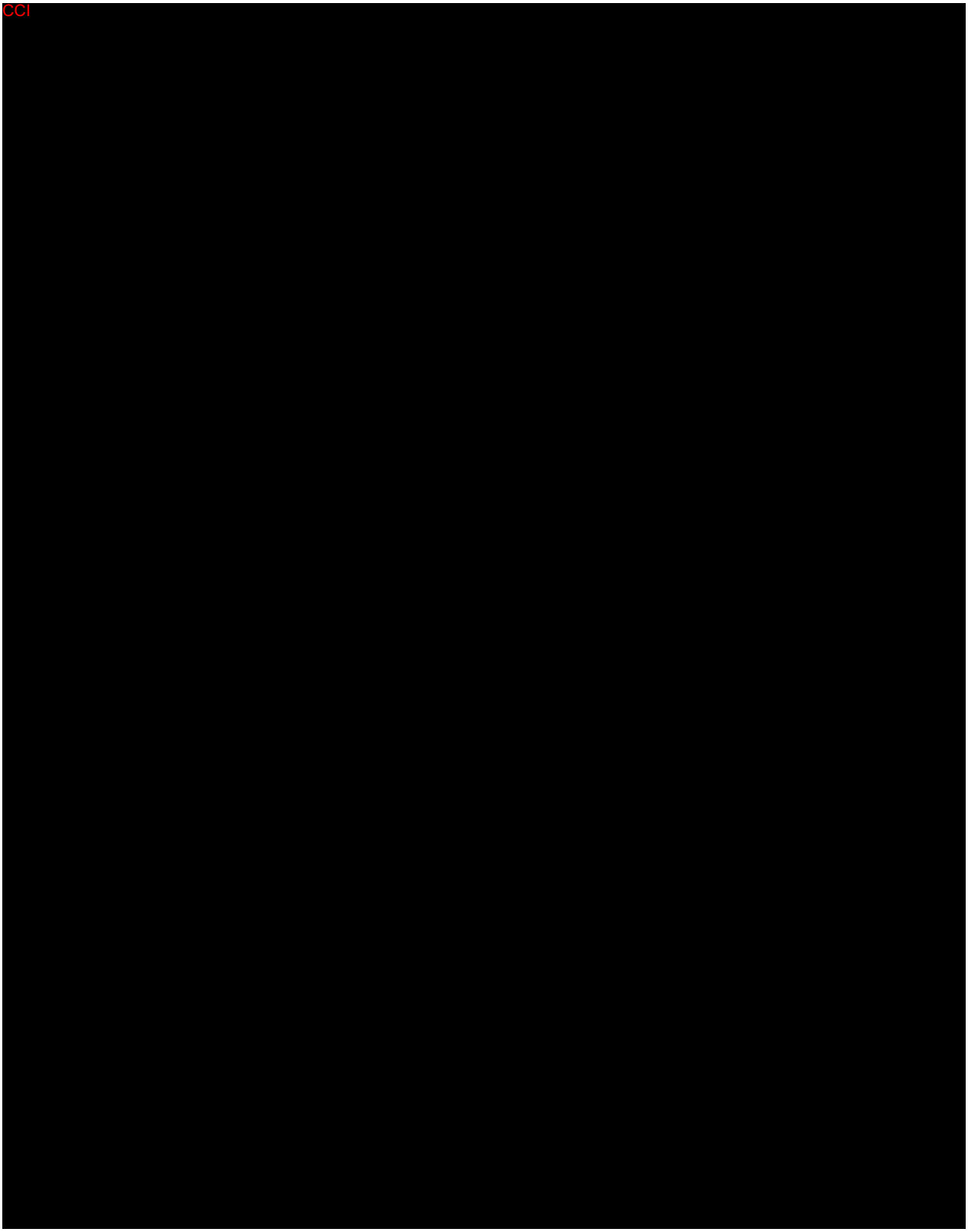
9.9 Sample Size and Power Calculations

The study enrollment has been completed with 1069 participants randomized in a 1:1 ratio into the pembrolizumab plus gemcitabine/cisplatin or placebo plus gemcitabine/cisplatin arms. OS is the sole primary endpoint for the study, with PFS and ORR as the key secondary endpoints.

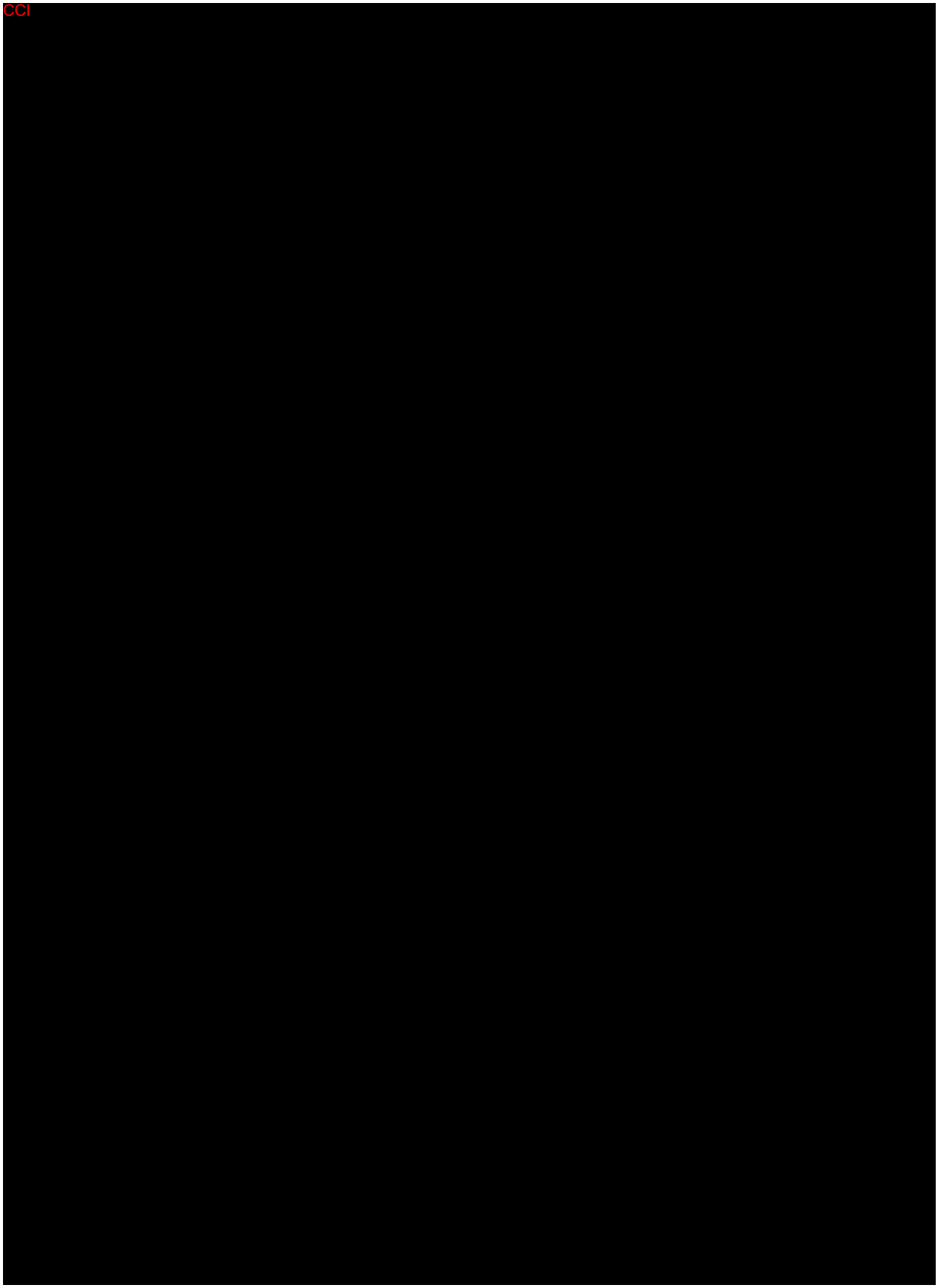
CCI

[redacted]

CCI



CCI



CCI

[redacted]

9.10 Subgroup Analyses

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

- Geographic region (Region 1: Asia versus Region 2: Non-Asia)
- Locally advanced versus metastatic
- Site of origin (gallbladder/intrahepatic/extrahepatic)
- Age category (<65, ≥65 years)
- Gender (female, male)
- Biliary stent and or a biliary drain (yes, no)
- Antibiotics within 1 month of study start (yes, no)
- Prior therapy (radiation, chemotherapy, PDT)
- Smoking status (never, former, current)
- Microsatellite instability-high (MSI-H) (yes, no, indeterminate)
- PD-L1 expression (CPS ≥1 versus <1)
- PD-L1 expression (CPS≥10 versus <10)
- ECOG performance status at randomization (0 vs. 1)

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is less than 5% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot. The subgroup analyses for PFS and OS will be conducted using

an unstratified Cox model, and the subgroup analyses for ORR will be conducted using the unstratified Miettinen and Nurminen method.

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, and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. 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 (or individuals acting on behalf of MSD) 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 fraud,

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee (SAC)

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

10.1.4.2 Executive Oversight Committee

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

10.1.4.3 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the 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 or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory with the exception of hepatitis testing, which will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 18 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Chemistry	Blood Urea Nitrogen (BUN)[a]	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[b]	Chloride	Phosphorous
	Creatinine[c]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
	Magnesium	Uric acid	Lactic Acid Dehydrogenase (LDH)	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Follicle stimulating hormone (as needed in women of nonchildbearing potential only) • Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP • Serology: Anti- HCV, HCV viral load, HBsAg, Anti-HBc (total and IgM), and HBV viral load, per local guidelines. See Appendix 7 for Country-Specific Requirements [e] • Serology HIV antibody (if required by local regulation) • Coagulation panel (PT/INR, aPTT) [f] • Thyroid function tests (T3 [or free T3[d]], free T4, and TSH) • Tuberculosis, if applicable (refer to Section 10.7 [Appendix 7] for country-specific requirements)			

Laboratory Assessments	Parameters
Abbreviations: ALT=alanine aminotransferase; Anti-HBc = hepatitis B core antibody; Anti-HCV= hepatitis C virus antibody; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HBsAg=hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV=human immunodeficiency virus; INR=International Normalized Ratio; PT=prothrombin time; RBC=red blood cell; RNA=ribonucleic acid; 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 childbearing potential a. Urea is acceptable if BUN is not available as per institutional standard. b. If the test is considered part of standard of care. c. Creatinine clearance can be used in place of creatinine (see Appendix 10 for calculation using Cockcroft and Gault Formula). d. T3 is preferred over free T3. If not available, free T3 may be tested. 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, HBsAg, Anti-HBc [total and IgM], and HBV viral load,) which will be performed centrally or locally as indicated in the protocol. f. PT/INR should be tested as needed for participants on warfarin-based anticoagulation therapy.	

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 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- 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.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

f. **Other important medical events**

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

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

10.3.3 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

10.3.4 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 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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 his/her best clinical judgment, including consideration of the above elements.

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

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

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

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

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

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

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

Follow-up of AE and SAE

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

10.3.5 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

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

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

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

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. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- CCI [redacted]

The specimen(s) may be used for CCI [redacted] CCI [redacted]

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

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, DNA, RNA, protein, 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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant's clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

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

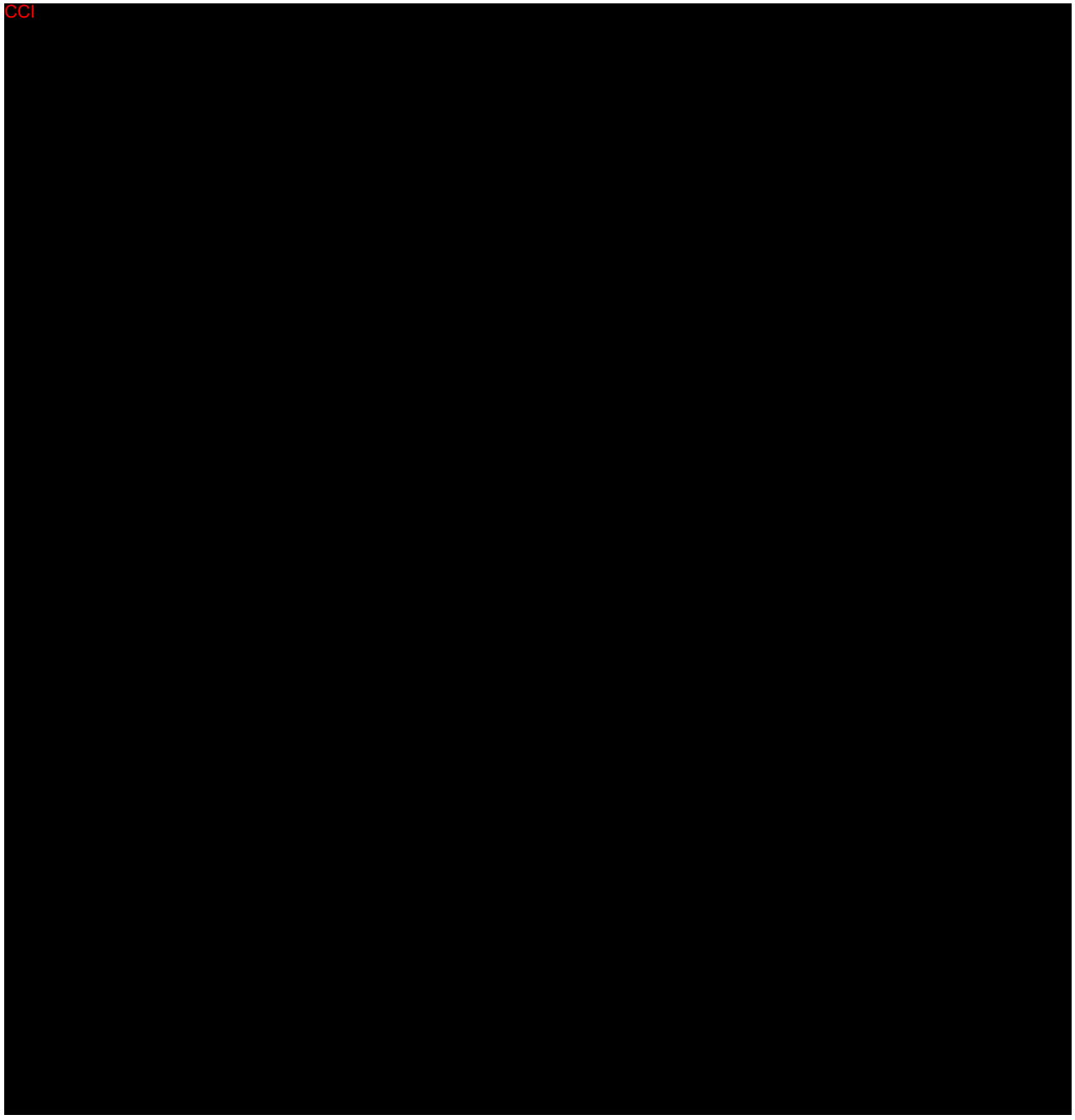
2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.htm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

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/

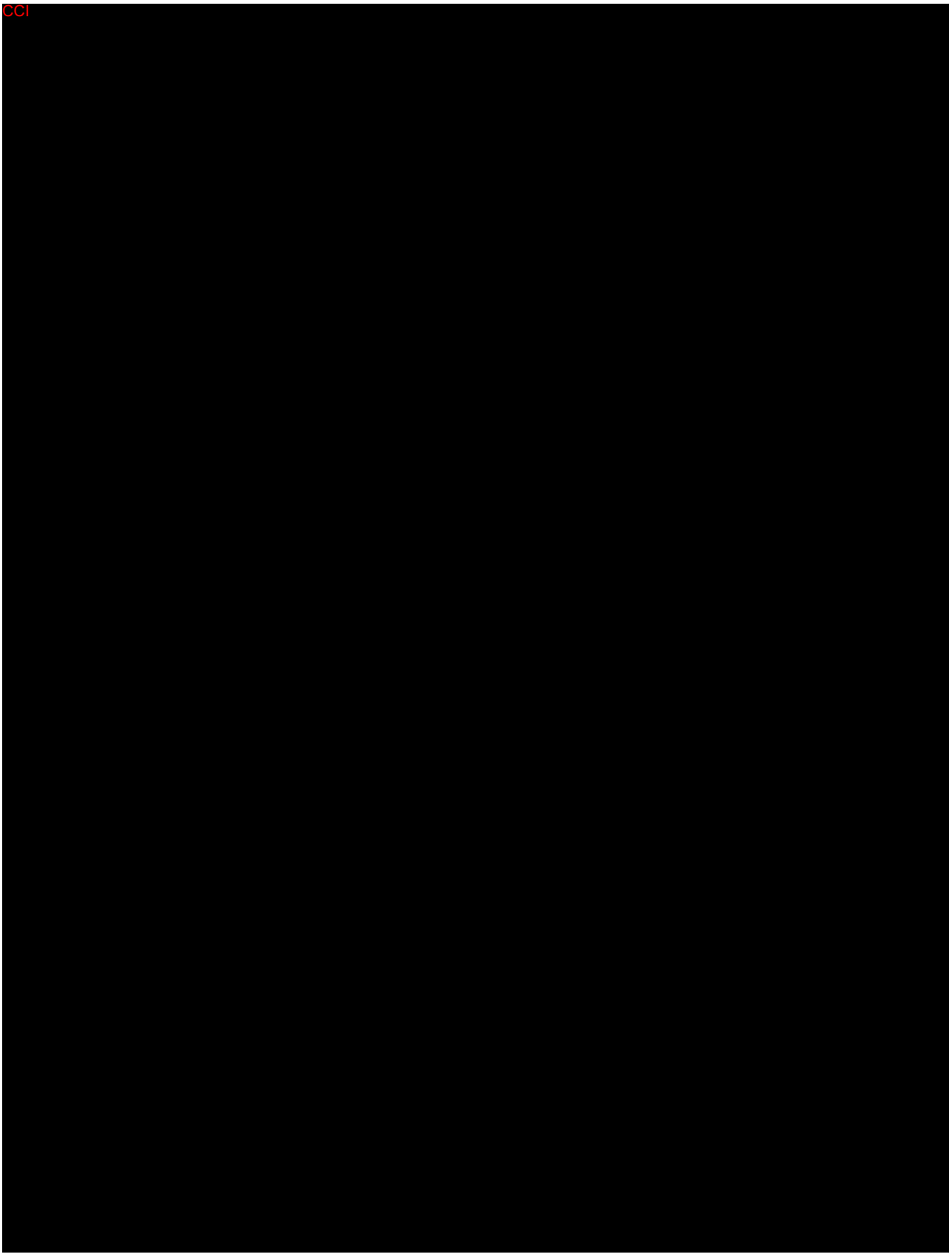
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

CCI



CCI



CCI

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

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and to guide decisions about changes in management.

Assessment at screening and before RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show radiological disease progression by RECIST 1.1, the investigator will decide whether to continue a participant on study intervention until repeat scans 4 to 8 weeks later are obtained, as described in Section 8.2.1.6.

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

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

- Unequivocal progression of nontarget lesion(s) identified at baseline

- Development of new lesion(s)

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

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

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

Assessment at the Confirmatory Scans

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Scan

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

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

Detection of Progression at Visits After Pseudo-progression Resolves

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

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

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

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

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

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

10.9 Appendix 9: ECOG Performance Status

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

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655
http://ecog-acrin.org/resources/ecog performance status

10.10 Appendix 10: Calculated Creatinine Clearance

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Men

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 1.0}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 1.0}{0.81 \times \text{serum creatinine (µmol/L)}}$$

Abbreviations: CrCl=creatinine clearance; wt=weight

a. Age in years.
b. Weight (wt) in kilograms.

Source: Cockcroft and Gault 1976. [Cockcroft, D. W. and Gault, M. H. 1976].

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Women

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 0.85}{0.81 \times \text{serum creatinine (µmol/L)}}$$

Abbreviations: CrCl=creatinine clearance; wt=weight

a. Age in years.
b. Weight (wt) in kilograms.

Source: Cockcroft and Gault 1976. [Cockcroft, D. W. and Gault, M. H. 1976].

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
Anti-HBe	hepatitis B e antibody
Anti-HBs	hepatitis B surface antibody
Anti-HCV	hepatitis C antibody
APaT	All Participants as Treated
ASC	active symptom control
AST	aspartate aminotransferase
BCG	*Bacillus* Calmette Guérin
BICR	blinded independent central review(er)
BSA	body surface area
BTC	biliary tract cancer
C	cycle
CCA	cholangiocarcinoma
CD	cluster of differentiation
CDE	Center for Drug Evaluation
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
D	day
D/C	discontinuation
DC	disease control
DCR	disease control rate
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group;
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency

Abbreviation	Expanded Term
EOC	Executive Oversight Committee
EOI	end of intervention
EORTC	European Organisation for the Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life 5-dimension, 5-level Questionnaire
ESMO	European Society for Medical Oncology
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin-embedded
FOLFOX	folinic acid, fluorouracil, and oxaliplatin
FSH	follicle stimulating hormone
FU	follow-up
GBC	gallbladder cancer
GCP	Good Clinical Practice
Gem/cis	gemcitabine/cisplatin
GEMOX	gemcitabine with oxaliplatin
H	hypothesis
HBc	hepatitis B core antibody
HBeAg	hepatitis B early antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	Hepatocellular cancer
HCV	hepatitis C virus
HECI	hepatic events of clinical interest
HGRAC	Human Genetics Resources Administration of China
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IA1	Interim analysis 1
IA2	Interim analysis 2
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	confirmed progressive disease per iRECIST
iCR	complete response per iRECIST
iCRO	imaging contract research organization
IDH1	isocitrate dehydrogenase 1
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
IO	immuno-oncology
iPR	partial response per iRECIST
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics

Abbreviation	Expanded Term
IRT	interactive response technology
iSD	stable disease per iRECIST
ITT	intention to treat
IUD	intrauterine device
IUO	investigational use only
iUPD	unconfirmed progressive disease per iRECIST
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	interactive voice response system
LDH	lactic acid dehydrogenase
LS	least squares
MASCC	Multinational Association of Supportive Care in Cancer
MMR	mismatch repair
M&N	Miettinen and Nurminen
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	Non-investigational Medicinal Product
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PDT	photodynamic therapy
PFS	progression-free survival
PK	pharmacokinetic
PO	*per os* (by mouth)
PR	partial response
PRO	patient-reported outcomes
PS	performance score
Q3/6/12W	every 3/6/12 weeks
QLQ	quality of life questionnaire
QOL	quality of life
R2	macroscopic residual tumor
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
S-1	oral fluoropyrimidine containing tegafur, gimeracil, and oteracil
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SIM	Site Imaging Manual
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
SoA	schedule of activities

Abbreviation	Expanded Term
SOC	standard of care
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TACE	transarterial chemoembolization
TARE	transarterial radioembolization
TB	tuberculosis
TILs	tumor-infiltrating lymphocytes
TSH	thyroid-stimulating hormone
TTD	time to deterioration
TTP	time-to-progression
UK	United Kingdom
ULN	upper limit of normal
US	United States
WOCBP	woman/women of childbearing potential

11 REFERENCES

[Aaronson, N. K., et al 1993]	Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.	[03Q3QL]
[Andre, T., et al 2004]	Andre T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F, Avenin D, et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol. 2004;15:1339-43.	[055GXL]
[Arbour, K. C., et al 2018]	Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. J Clin Oncol. 2018 Oct 1;36(28):2872-8.	[053NJK]
[Balar, A. V., et al 2017]	Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017 Jan 7;389:67-76. Erratum in: Lancet. 2017 Aug 26;390:848.	[052J9H]
[Banales, J. M., et al 2016]	Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol. 2016 May;13:261-80.	[057340]

[Bang, Y. J., et al 2015]	Bang YJ, Doi T, De Braud F, Piha-Paul S, Hollebecque A, Abdul Razak AR, et al. Safety and efficacy of pembrolizumab (MK-3475) in patients (pts) with advanced biliary tract cancer: Interim results of KEYNOTE-028. Poster session presented at European Cancer Congress (ECCO); 2015 September 25-29; Vienna, AT.	[04QTFG]
[Bang, Y. J., et al 2019]	Bang YJ, Kang YK, Catenacci DV, Muro K, Fuchs CS, Geva R, et al. Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the phase II nonrandomized KEYNOTE-059 study. Gastric Cancer. 2019;22:828-37.	[05NM98]
[Bragazzi, M. C., et al 2012]	Bragazzi MC, Cardinale V, Carpino G, Venere R, Semeraro R, Gentile R, et al. Cholangiocarcinoma: epidemiology and risk factors. Transl Gastrointest Cancer. 2012 Apr;1(1):21-32.	[054YR7]
[Burtness, B., et al 2019]	Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G Jr, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019 Nov 23;394:1915-28.	[05CTJX]
[Chan-On, W., et al 2013]	Chan-On W, Nairismagi ML, Ong CK, Lim WK, Dima S, Pairojkul C, et al. Exome sequencing identifies distinct mutational patterns in liver fluke-related and non-infection-related bile duct cancers. Nat Genet. 2013 Dec;45(12):1474-8.	[054PRN]

[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Clopper, C. J. 1934]	Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03Y75Y]
[Cockcroft, D. W. and Gault, M. H. 1976]	Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.	[03R5YC]
[Cubas, R., et al 2018]	Cubas R, Moskalenko M, Cheung J, Yang M, McNamara E, Xiong H, et al. Chemotherapy combines effectively with anti-PD-L1 treatment and can augment antitumor responses. J Immunol. 2018;201:2273-86.	[058576]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Edeline, J., et al 2019]	Edeline J, Benabdelghani M, Bertaut A, Watelet J, Hammel P, Joly JP, et al. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): a randomized phase III study. J Clin Oncol. 2019;37(8):658-67.	[05NM9C]

[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Galsky, M. D., et al 2018]	Galsky MD, Wang H, Hahn NM, Twardowski P, Pal SK, Albany C, et al. Phase 2 trial of gemcitabine, cisplatin, plus ipilimumab in patients with metastatic urothelial cancer and impact of DNA damage response gene mutations on outcomes. Eur Urol. 2018;73:751-9.	[05856T]
[Gao, F., et al 2010]	Gao F, Bai Y, Ma SR, Liu F, Li ZS. Systematic review: photodynamic therapy for unresectable cholangiocarcinoma. J Hepatobiliary Pancreat Sci. 2010;17:125-31.	[056DHH]
[Goeppert, B., et al 2013]	Goeppert B, Frauenschuh L, Zucknick M, Stenzinger A, Andrulis M, Klauschen F, et al. Prognostic impact of tumour-infiltrating immune cells on biliary tract cancer. Br J Cancer. 2013;109:2665-74.	[055P3R]
[Gou, M., et al 2019]	Gou M, Zhang Y, Si H, Dai G. Efficacy and safety of nivolumab for metastatic biliary tract cancer. Onco Targets Ther. 2019;12:861-7.	[055X8L]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Han, K., et al 2015]	Han K, Ko HK, Kim KW, Won HJ, Shin YM, Kim PN. Radiofrequency ablation in the treatment of unresectable intrahepatic cholangiocarcinoma: systematic review and meta-analysis. J Vasc Interv Radiol. 2015 Jul;26(7):943-8.	[056DHZ]

[Hatzaras, I., et al 2010]	Hatzaras I, George N, Muscarella P, Melvin WS, Ellison EC, Bloomston M. Predictors of survival in periampullary cancers following pancreaticoduodenectomy. Ann Surg Oncol. 2010;17:991-7.	[055TPG]
[He, S., et al 2014]	He S, Shen J, Sun X, Liu L, Dong J. A phase II FOLFOX-4 regimen as second-line treatment in advanced biliary tract cancer refractory to gemcitabine/cisplatin. J Chemother. 2014;26(4):243-7.	[056DJ8]
[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Horn, L., et al 2018]	Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018 Dec 6;379(23):2220-9.	[054CCC]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]

[Ikeda, M., et al 2019]	Ikeda M, Ueno M, Morizane C, Kobayashi S, Ohno I, Kondo S, et al. A multicenter, open-label, phase I study of nivolumab alone or in combination with gemcitabine plus cisplatin in patients with unresectable or recurrent biliary tract cancer [abstract]. Presented at: American Society of Clinical Oncology (ASCO) 2019 Gastrointestinal Cancers Symposium; 2019 Jan 17-19; San Francisco, CA. J Clin Oncol. 2019;37(suppl 4). Abstract no. 306.	[055GXQ]
[Ioka, T., et al 2019]	Ioka T, Ueno M, Oh DY, Fujiwara Y, Chen JS, Doki Y, et al. Evaluation of safety and tolerability of durvalumab (D) with or without tremelimumab (T) in patients (pts) with biliary tract cancer (BTC) [abstract]. Presented at: American Society of Clinical Oncology (ASCO) 2019 Gastrointestinal Cancers Symposium; 2019 Jan 17-19; San Francisco, CA. J Clin Oncol. 2019;37(suppl 4). Abstract no. 387.	[055GXR]
[Javle, M., et al 2015]	Javle M, Churi C, Kang HC, Shroff R, Janku F, Surapaneni R, et al. HER2/neu-directed therapy for biliary tract cancer. J Hematol Oncol. 2015;8:58.	[055X8N]
[Kazandjian, D., et al 2016]	Kazandjian D, Suzman DL, Blumenthal G, Mushti S, He K, Libeg M, et al. FDA Approval Summary: Nivolumab for the Treatment of Metastatic Non-Small Cell Lung Cancer With Progression On or After Platinum-Based Chemotherapy. Oncologist. 2016 May;21(5):634-42.	[04MYTV]

[Kim, R., et al 2018]	Kim R, Kim D, Alese O, Li D, El-Rayes B, Shah N, et al. A phase II multi institutional study of nivolumab in patients with advanced refractory biliary tract cancers (BTC) [abstract]. Presented at: European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer; 2018 Jun 20-23; Barcelona (Spain). Ann Oncol. 2018;29(suppl 5):v103. Abstract no. O-009.	[055P6G]
[Kim, S., et al 2002]	Kim S, Kim SW, Bang YJ, Heo DS, Ha SW. Role of postoperative radiotherapy in the management of extrahepatic bile duct cancer. Int J Radiat Oncol Biol Phys. 2002;54(2):414-9.	[055GXM]
[Lazcano-Ponce, E. C., et al 2001]	Lazcano-Ponce EC, Miquel JF, Munoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin. 2001 Nov-Dec;51(6):349-64.	[055GXN]
[Le, D. T., et al 2017]	Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017 Jul 28;357:409-13.	[055GXK]
[Lynch, S. V. 2016]	Lynch SV, Pedersen O. The Human Intestinal Microbiome in Health and Disease. N Engl J Med. 2016 Dec 15;375(24):2369-2379.	[04PZSF]
[Margonis, G. A., et al 2016]	Margonis GA, Gani F, Buettner S, Amini N, Sasaki K, Andreatos N, et al. Rates and patterns of recurrence after curative intent resection for gallbladder cancer: a multi-institution analysis from the US Extra-hepatic Biliary Malignancy Consortium. HPB (Oxford). 2016;18:872-8.	[055GXP]

[Maurer, W., et al 2011]	Maurer W, Glimm E, Bretz F. Multiple and repeated testing of primary, coprimary, and secondary hypotheses. Stat Biopharm Res. 2011;3(2):336-52.	[045MYM]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[Mizusawa, J., et al 2016]	Mizusawa J, Morizane C, Okusaka T, Katayama H, Ishii H, Fukuda H, et al. Randomized Phase III study of gemcitabine plus S-1 versus gemcitabine plus cisplatin in advanced biliary tract cancer: Japan Clinical Oncology Group Study (JCOG1113, FUGA-BT). Jpn J Clin Oncol. 2016;46(4):385-8.	[055GXT]
[Nakamura, H., et al 2015]	Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, et al. Genomic spectra of biliary tract cancer. Nat Genet. 2015 Sep;47(9):1003-10.	[054PRT]
[Nakeeb, A. 2005]	Nakeeb A, Pitt HA. Radiation therapy, chemotherapy and chemoradiation in hilar cholangiocarcinoma. HPB (Oxford). 2005;7:278-82.	[055P5C]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Okusaka, T., et al 2010]	Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer. 2010 Aug 10;103(4):469-74.	[045N25]

[Osoba, D., et al 1998]	Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-44.	[00TWVP]
[Ott, P. A., et al 2018]	Ott PA, Bang YJ, Piha-Paul SA, Razak ARA, Bennouna J, Soria JC, et al. T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. J Clin Oncol. 2018;37(4):318-27.	[0579JP]
[Papadimitrakopoulou, V., et al 2015]	Papadimitrakopoulou V, Patnaik A, Borghaei H, Stevenson J, Gandhi L, Gubens MA, et al. Pembrolizumab (pembro; MK-3475) plus platinum doublet chemotherapy (PDC) as front-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohorts A and C [abstract]. J Clin Oncol. 2015 May 29;33(Suppl). Abstract no. 8031.	[04CT06]
[Park, I., et al 2009]	Park I, Lee JL, Ryu MH, Kim TW, Lee SS, Park DH, et al. Prognostic factors and predictive model in patients with advanced biliary tract adenocarcinoma receiving first-line palliative chemotherapy. Cancer. 2009 Sep 15;115:4148-55.	[055TPK]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Pickard, A. S., et al 2007]	Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:1-8.	[00W0FM]

[Pölcher, M., et al 2010]	Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59(6):909-19.	[00VMQ8]
[Primrose, J. N., et al 2019]	Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol. 2019 May;20:663-73.	[05NM9D]
[Rabin, R. 2001]	Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43.	[03QM46]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Robert, C., et al 2011]	Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364(26):2517-26.	[058SQS]
[Ropponen, K. M., et al 1997]	Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997;182(3):318-24.	[00VMQT]
[Sahai, V., et al 2018]	Sahai V, Catalano PJ, Zalupski MM, Lubner SJ, Menge MR, Nimeiri HS, et al. Nab-paclitaxel and gemcitabine as first-line treatment of advanced or metastatic cholangiocarcinoma: a phase 2 clinical trial. JAMA Oncol. 2018 Dec;4(12):1707-12.	[05734P]

[Sapisochin, G., et al 2015]	Sapisochin G, Fernandez de Sevilla E, Echeverri J, Charco R. Liver transplantation for cholangiocarcinoma: current status and new insights. World J Hepatol. 2015 Oct 8;7(22):2396-403.	[057354]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Shibata, T., et al 2018]	Shibata T, Arai Y, Totoki Y. Molecular genomic landscapes of hepatobiliary cancer. Cancer Sci. 2018;109:1282-91.	[054PS9]
[Shin, H. R., et al 2010]	Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang Y, et al. Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma - focus on East and South-eastern Asia. Asian Pac J Cancer Prev. 2010;11:1159-66.	[054YZW]
[Shitara, K., et al 2020]	Shitara K, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. JAMA Oncol. 2020 Oct;6(10):1571-80.	[05N2MK]
[Siegel, R. L., et al 2018]	Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018 Jan-Feb;68(1):7-30.	[04Y4JF]

[Socinski, M. A., et al 2018]	Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018 Jun 14;378(24):2288-301.	[052QQF]
[Tajima, H., et al 2017]	Tajima H, Ohta T, Shinbashi H, Hirose A, Okazaki M, Yamaguchi T, et al. Phase I study of weekly palliative chemotherapy with low-dose third-line paclitaxel for biliary tract cancer. Mol Clin Oncol. 2017;6:753-7.	[05734G]
[Ueno, M., et al 2018]	Ueno M, Chung HC, Nagrial A, Marabelle A, Kelley RK, Xu L, et al. Pembrolizumab for advanced biliary adenocarcinoma: results from the multicohort, phase II KEYNOTE-158 study [abstract]. Presented at: European Society for Medical Oncology (ESMO) 2018 Congress; 2018 Oct 19-23; Munich (Germany). Ann Oncol. 2018;29(suppl 8):viii210. Abstract no. 625PD.	[055P6N]
[Ueno, M., et al 2019]	Ueno M, Ikeda M, Morizane C, Kobayashi S, Ohno I, Kondo S, et al. Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study. Lancet Gastroenterol Hepatol. 2019 Aug;4:611-21.	[05NN88]
[Valle, J., et al 2010]	Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81.	[045N35]

[Venook, A. P., et al 2000]	Venook AP, Egorin MJ, Rosner GL, Hollis D, Mani S, Hawkins M, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. J Clin Oncol. 2000 Jul;18(14):2780-7.	[057TX0]
[Wang, Y., et al 2017]	Wang Y, Ding M, Zhang Q, Wang J, Yang X, Zhou F, et al. Activation or suppression of the immune response mediators in biliary tract cancer (BTC) patients: a systematic review and meta-analysis. J Cancer. 2017;8(1):74-84.	[054Z06]
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[Yang, J. C., et al 2013]	Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TSK, et al. Symptom control and quality of life in LUX-Lung 3: A phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31(27):3342-50.	[03NDT4]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]
[Zhu, A. X., et al 2010]	Zhu AX, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. Oncologist. 2010;15:168-81.	[055GXW]