2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereafter called the Sponsor or MSD)

COMPOUND NAME: Pembrolizumab (MK-3475)

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

STUDY IDENTIFIERS:

IND: 123482	EudraCT: 2019-000944-82	WHO: Not applicable	NCT: NCT04003636
JAPIC-CTI: Not applicable	UTN: Not applicable	EU CT: Not applicable	

STUDY PHASE: Phase 3

INDICATION: Biliary tract carcinoma

STUDY CENTERS: This study was conducted at 185 centers in 24 countries/regions.

STUDY STATUS:

This study is ongoing; this report is based on the FA.

First Participant, First Visit	**Data Cut-off**	**Database Lock Date**
24-SEP-2019	15-DEC-2022	19-JAN-2023

METHODOLOGY:

This is a randomized, placebo-controlled, parallel-group, multisite, double-blind study of pembrolizumab plus chemotherapy (gemcitabine plus cisplatin) versus placebo plus chemotherapy (gemcitabine plus cisplatin) in participants with advanced (metastatic) and/or unresectable (locally advanced) BTC (intra- or extrahepatic cholangiocarcinoma or gallbladder) (hereafter referred to as advanced BTC).

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	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

IV=intravenous, N/A=not applicable; PD=disease progression, Q3W=every 3 weeks.

Part of this study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its Standard Operating Procedures for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

ELIGIBILITY CRITERIA:

Male and female participants at least 18 years of age who had a histologically confirmed diagnosis of advanced BTC, measurable disease per RECIST 1.1, no prior systemic therapy, with the exception of neoadjuvant/adjuvant therapy, and an ECOG performance status 0 or 1 were included. Participants with controlled HBV and past or ongoing HCV infection were eligible for the study.

OBJECTIVES AND ENDPOINTS:

The following objectives and endpoints listed were for 1L therapy of participants with advanced and/or unresectable BTC:

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
• 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)

Objectives	Endpoints
• 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

NOTE: Although the original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, throughout the 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 of the study protocol for further details.

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 1048 participants. As of the 15-DEC-2022 data cutoff, 1069 participants were randomized: 533 to pembrolizumab plus gemcitabine/cisplatin (hereafter referred to as "pembrolizumab plus chemotherapy group") and 536 to placebo plus gemcitabine plus cisplatin (hereafter referred to as the "placebo plus chemotherapy group").

STATISTICAL AND ANALYSIS METHODS:

The analyses of efficacy endpoints other than DOR were based on the ITT population, which included all randomized participants. The DOR analysis was based on the population of responders (participants who achieved confirmed CR or PR). The study uses the graphical method of Maurer and Bretz to control Type I error across multiple hypotheses (OS, PFS, and ORR) as well as interim analyses. The primary and secondary PFS hypotheses were 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 was performed using a stratified Cox regression model with Efron's method of tie handling. Event rates over time were estimated within each intervention group using the Kaplan-Meier method. The stratified Miettinen and Nurminen method with strata weighted by sample size was used for analysis of ORR. The efficacy analyses for ORR, DOR and PFS include responses and documented progression events that occurred before the second course treatment.

The FA was to be performed when ~818 OS events had been observed and ~38 months had passed since the start of randomization. The primary endpoint of OS was analyzed based on FA data (as of the data cutoff date of 15-DEC-2022). The analyses of PFS, ORR, and DOR (secondary endpoints) were prespecified in the protocol to be based on IA1 data (as of the

data cutoff date of 15-DEC-2021). Descriptive statistics for these PFS, ORR and DOR at FA were also provided.

All *p*-values in efficacy analyses are one-sided except for analyses of PRO endpoints where two-sided *p*-values are provided.

The safety analyses were conducted using APaT population, which included all randomized participants who received at least 1 dose of study intervention. The analysis of safety results followed a tiered approach. The tiers differed with respect to the analyses that were performed. AEs (specific terms as well as system organ class terms) were either prespecified as "Tier 1" endpoints or classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. AEs that are immune-mediated or potentially immune-mediated were well documented and were 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. The Miettinen and Nurminen method was used for analyses in which 95% CIs are provided.

The PRO analyses were based on the PRO FAS population, defined as participants who had received at least 1 dose of study intervention and had completed at least 1 PRO assessment.

RESULTS:

Participant Disposition:

- Pembrolizumab plus chemotherapy: 533 randomized, 529 treated, 13 completed treatment, 489 discontinued treatment, 27 ongoing on treatment, 414 discontinued study, 119 ongoing in the study.
- Placebo plus chemotherapy: 536 randomized, 534 treated, 7 completed treatment, 504 discontinued treatment, 23 ongoing on treatment, 446 discontinued study, 90 ongoing in the study.

Demographics and Baseline Characteristics:

- **Overall Median Age (range):** 64.0 years (23 to 85 years)

Sex: 522 (51.6%) male, 517 (48.4%) female

Ethnicity: 882 (82.5%) not Hispanic or Latino, 111 (10.4%) Hispanic or Latino, 76 (7.1%) not reported/unknown/missing

Race: 524 (49.0%) white, 495 (46.3%) Asian, 14 (1.3%) black or African American, 7 (0.7%) multiple, 3 (0.3%) American Indian or Alaska Native, 25 (2.3%) not reported/unknown/missing

Efficacy:

Primary Endpoint

OS results based on the FA (DCO 15-DEC-2022):

- Pembrolizumab in combination with chemotherapy provided a therapeutic benefit to participants with advanced BTC as shown by improvement in OS compared with placebo plus chemotherapy.
- Treatment with pembrolizumab plus chemotherapy met the primary endpoint prespecified criteria for statistical significance and resulted in a clinically meaningful improvement in OS compared with placebo plus chemotherapy (HR 0.83 [95% CI: 0.72, 0.95; *p*=0.0034] which is below the *p*-value boundary for FA of 0.0200). The median OS was 12.7 months (95% CI: 11.5, 13.6) in the pembrolizumab plus chemotherapy group and 10.9 months (95% CI: 9.9, 11.6) in the placebo plus chemotherapy group.
- The KM curves for OS showed clear separation starting at approximately 2 months and remained consistently separated throughout the evaluation period in favor of the pembrolizumab plus chemotherapy group.
- OS rate at 12 and 24 months was higher in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group (51.6% vs 44.1% at 12 months and 24.9% vs 18.1% at 24 months).

Secondary Endpoints

The analyses of PFS, ORR and DOR were prespecified in the protocol to occur at IA1 (DCO 15-DEC-2021) with the following results:

- There was a positive trend in PFS with pembrolizumab plus chemotherapy but the results did not meet the prespecified criteria for statistical significance for PFS when compared with placebo plus chemotherapy based on BICR assessment per RECIST 1.1. (HR 0.86 [95% CI: 0.75, 1.00; *p*=0.0225 which is above the *p*-value boundary of 0.0125]).
- The median PFS was 6.5 months (95% CI: 5.7, 6.9) in the pembrolizumab plus chemotherapy group and 5.6 months (95% CI: 5.1, 6.6) in the placebo plus chemotherapy group.
- The KM curves for PFS showed separation starting at approximately 3 months and remained consistently separated throughout the evaluation period in favor of the pembrolizumab plus chemotherapy group.
- PFS rate at 12 and 18 months as assessed by BICR per RECIST 1.1 was higher in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group (25.4% vs 19.8% at 12 months and 11.9% vs 8.4% at 18 months).
- Treatment with pembrolizumab plus chemotherapy did not meet the prespecified criteria for statistical significance in ORR when compared with chemotherapy alone based on BICR assessment by RECIST 1.1. The confirmed ORR was 28.7% (95% CI: 24.9, 32.8) with pembrolizumab plus chemotherapy and 28.5% (95% CI: 24.8, 32.6) with placebo plus chemotherapy.

- Among responders, the DOR was longer in the pembrolizumab plus chemotherapy group with a median of 9.7 months (range 1.2+ to 22.7+ months) compared with 6.9 months (0.0+ to 19.2+ months) in the placebo plus chemotherapy group.
- From baseline to Week 18, HRQoL was maintained when pembrolizumab was added to chemotherapy.

Safety:

- The safety results of pembrolizumab in combination with chemotherapy in previously untreated participants with advanced BTC was generally consistent with the known safety profiles of pembrolizumab monotherapy and chemotherapy, and/or with the underlying disease (eg, anticipated hepatobiliary AEs).
  - The addition of pembrolizumab to chemotherapy did not result in an increase in either the incidence or severity of common chemotherapy-related toxicities (eg, drug-related AEs, Grade 3 to 5, SAEs, deaths).
  - Incidence of deaths in the study due to AEs was similar between the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups (5.9% vs 9.2%).
  - Incidence of treatment discontinuations due to AEs was similar between the 2 groups.
  - Observed toxicities were generally manageable with standard medical care, drug discontinuation/interruption, or corticosteroid use for pembrolizumab AEOSI as appropriate.
  - The incidence of AEOSI was as expected in the pembrolizumab plus chemotherapy group compared with placebo plus chemotherapy group, and was consistent with the incidence of AEOSI seen in participants treated with pembrolizumab monotherapy. AEOSI were manageable with treatment discontinuation/interruption, corticosteroids, and supportive care as appropriate. The nature, management, and outcome of AEOSI between the 2 treatment groups remained unchanged.
  - Addition of pembrolizumab to chemotherapy did not demonstrate increased risk of viral hepatitis flare in the BTC population with preexisting HBV/HCV.
  - The incidence of HECI was generally similar between the 2 study groups and the addition of pembrolizumab to chemotherapy did not demonstrate an increased risk of HECI.
  - No new safety concerns were identified for pembrolizumab.

Adverse Event Summary
(APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	529		534	
with one or more adverse events	524	(99.1)	532	(99.6)
with no adverse event	5	(0.9)	2	(0.4)
with drug-related[a] adverse events	493	(93.2)	500	(93.6)
with toxicity grade 3-5 adverse events	451	(85.3)	449	(84.1)
with toxicity grade 3-5 drug-related adverse events	377	(71.3)	370	(69.3)
with serious adverse events	276	(52.2)	263	(49.3)
with serious drug-related adverse events	121	(22.9)	84	(15.7)
who died	31	(5.9)	49	(9.2)
who died due to a drug-related adverse event	8	(1.5)	3	(0.6)
discontinued any drug due to an adverse event	138	(26.1)	122	(22.8)
discontinued MK-3475/PLACEBO	77	(14.6)	66	(12.4)
discontinued any chemotherapy	124	(23.4)	113	(21.2)
discontinued all drugs	35	(6.6)	39	(7.3)
discontinued any drug due to a drug-related adverse event	102	(19.3)	81	(15.2)
discontinued MK-3475/PLACEBO	47	(8.9)	26	(4.9)
discontinued any chemotherapy	90	(17.0)	73	(13.7)
discontinued all drugs	18	(3.4)	14	(2.6)
discontinued any drug due to a serious adverse event	76	(14.4)	61	(11.4)
discontinued MK-3475/PLACEBO	61	(11.5)	54	(10.1)
discontinued any chemotherapy	67	(12.7)	52	(9.7)
discontinued all drugs	30	(5.7)	33	(6.2)
discontinued any drug due to a serious drug-related adverse event	41	(7.8)	20	(3.7)
discontinued MK-3475/PLACEBO	32	(6.0)	14	(2.6)
discontinued any chemotherapy	35	(6.6)	17	(3.2)
discontinued all drugs	14	(2.6)	8	(1.5)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 5.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15DEC2022.

CONCLUSIONS:

Efficacy

Based on the results from this study, the following efficacy conclusions can be made:

- Pembrolizumab in combination with chemotherapy in 1L provides a therapeutic benefit to patients with advanced BTC as shown by a statistically significant and clinically meaningful improvement in OS compared with chemotherapy alone.

- There was a positive trend in PFS per RECIST 1.1 by BICR in treatment with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy, but the results did not meet the prespecified criteria for statistical significance.
- Treatment with pembrolizumab plus chemotherapy did not meet the prespecified criteria for statistical significance in ORR when compared with chemotherapy alone based on BICR assessment by RECIST 1.1.
- Treatment with pembrolizumab plus chemotherapy provided responders with an extended DOR compared with the placebo plus chemotherapy group, which was retained with additional follow-up through the FA.

Safety

Based on the results from this study, the following safety conclusions can be made:

- The safety profile of pembrolizumab, in combination with chemotherapy, is consistent with the known safety profiles of individual chemotherapies and pembrolizumab monotherapy and/or with the underlying disease. No new safety concern has been identified.
- No new indication-specific immune-mediated AEs have been identified when pembrolizumab was administered concurrently with chemotherapy.
- AEOSI are manageable with treatment discontinuation/interruption, corticosteroid use and/or supportive care.
- Treatment with pembrolizumab, in combination with chemotherapy, is generally tolerable.

List of Abbreviations

Abbreviation/Term	Definition
1L	first line
AE	adverse event
AEOSI	adverse event of special interest
APaT	all participants as treated
BICR	blinded independent central review(er)
BTC	biliary tract carcinoma
CI	confidence interval
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CR	complete response
DCO	data cutoff
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FA	final analysis
FAS	full analysis set
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HECI	hepatic events of clinical interest
HR	hazard ratio
IA1	interim analysis 1
ITT	intent-to-treat
KM	Kaplan-Meier
MSD	Merck Sharp & Dohme LLC, Rahway, NJ, USA
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
PRO	patient-reported outcomes
RECIST	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event

Abbreviation/Term	Definition
SD	stable disease

PUBLICATIONS: Finn RS, Kelley RK, Furuse J, Edeline J, Ren Z, Su SC, et al. KEYNOTE-966: A randomized, double-blind, placebo-controlled, phase 3 study of pembrolizumab in combination with gemcitabine and cisplatin for the treatment of advanced biliary tract carcinoma. Cancer Res. 2020;80(Suppl 16):CT283.

Kelley RK, Vogel A, Finn RS, Furuse J, Edeline J, Ren Z, et al. Pembrolizumab in Combination With Gemcitabine and Cisplatin for the Treatment of Advanced Biliary Tract Cancer: Phase 3 KEYNOTE-966 Trial in Progress. In: Proceedings from International Liver Cancer Association - 14th Annual Conference. 2020; ILCA Book of Abstracts.

Kelley RK, Vogel A, Furuse J, Edeline J, Finn RS, Ren Z, et al. KEYNOTE-966 Trial in Progress: Pembrolizumab added to Gemcitabine and Cisplatin for Advanced Biliary Tract Cancer. The Liver Meeting - 71st Annual Meeting of the American Association for the Study of Liver Diseases. 2020;72(S1):697A.

Valle J, Kelley RK, Furuse J, Edeline J, Finn RS, Ren Z, et al. KEYNOTE-966 trial in progress: pembrolizumab plus gemcitabine and cisplatin for advanced biliary tract cancer. European Society for Medical Oncology 45th Congress - ESMO 2020. 2020; Epub ahead of final.

Vogel A, Finn RS, Kelley RK, Furuse J, Edeline J, Ren Z, et al. Pembrolizumab in combination with gemcitabine and cisplatin for the treatment of advanced biliary tract cancer: phase 3 KEYNOTE-966 trial in progress. Annals of Oncology. 2020;31(Supp 3):S122.

REPORT DATE: 20-MAR-2023

REVISED REPORT DATE: 19-JAN-2024