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; NCT04924062 (China extension)
UTN: Not applicable	EU CT: Not applicable	CDE: CTR20192713	

STUDY PHASE: Phase 3

INDICATION: Biliary tract carcinoma

STUDY CENTERS: This study was conducted at 185 centers in 24 countries/regions worldwide, including 23 centers in China.

STUDY STATUS: This study is ongoing; this report is based on the FA of the China subpopulation as of 15-DEC-2022 DCO, which is the same as the DCO for the FA of the global population.

First Participant, First Visit (China)	**Data Cut-off**	**Database Lock Date**
10-JUL-2020	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

China refers to China Mainland in this document.

unresectable (locally advanced) BTC (intra- or extrahepatic cholangiocarcinoma or gallbladder) (hereafter referred to as advanced BTC). After the enrollment for the global portion was completed, participants in China continued to be enrolled until the sample size for the China subpopulation reached approximately 158 in total of global portion and China extension portion combined to meet local regulatory requirements. China extension portion of the study was identical to the global portion (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, and study procedures), with the exception of an additional statistical analysis plan for the China subpopulation. Details of the analysis plan was provided in a separate supplemental statistical analysis plan.

Intervention 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

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:

No hypothesis testing was planned for the China subpopulation analyses. The objectives and endpoints for the study were as follows:

Objectives	Endpoints
Primary	
• Objective: To compare overall survival (OS) between pembrolizumab plus gemcitabine/cisplatin and placebo plus gemcitabine/cisplatin	• 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	• 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	• 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

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 total planned enrollment in China was 158 participants in the global portion and the China extension portion of the study combined. As of the 15-DEC-2022 data cut off, 158 China participants were randomized: 75 to pembrolizumab plus gemcitabine/cisplatin (hereafter referred to as "pembrolizumab plus chemotherapy group") and 83 to placebo plus gemcitabine plus cisplatin (hereafter referred to as the "placebo plus chemotherapy group"). Among them, 112 were randomized in the global portion and 46 were randomized in China extension portion.

STATISTICAL AND ANALYTICAL METHODS:

The purpose of this analysis report was to evaluate the consistency of efficacy and safety in the China subpopulation with the global population. No formal hypothesis testing was planned for China subpopulation. No multiplicity adjustment was applied to the analysis of the China subpopulation. All analyses in the China subpopulation were descriptive.

The analyses of efficacy endpoints other than DOR were based on the China ITT population, which included all China randomized participants in the global portion and the China extension portion. The DOR analysis was based on the China subpopulation of responders (participants who achieved confirmed CR or PR). The non-parametric Kaplan-Meier method was used to estimate the OS and PFS curves respectively. An unstratified Cox proportional hazard model with Efron's method of tie handling was used to estimate the magnitude of the treatment difference (ie, HR) between the intervention groups. The unstratified Miettinen and Nurminen method was used for analysis of ORR. The efficacy analyses for ORR, DOR and PFS included responses and documented progression events that occurred before the second course treatment.

The primary endpoint of OS and the secondary endpoints of PFS, ORR, and DOR were analyzed based on the China subpopulation data as of the DCO of FA (15-DEC-2022).

The safety analyses were conducted using all China APaT population, which included all China randomized participants who received at least 1 dose of study intervention in the global portion and China extension portion. The Miettinen and Nurminen method was used for analyses in which 95% CIs are provided.

RESULTS:

Participant Disposition:

- Pembrolizumab plus chemotherapy: 75 randomized, 74 treated, 65 discontinued treatment, 9 ongoing on treatment, 49 discontinued study, 26 ongoing in the study.
- Placebo plus chemotherapy: 83 randomized, 82 treated, 78 discontinued treatment, 4 ongoing on treatment, 63 discontinued study, 20 ongoing in the study.

Demographics and Baseline Characteristics:

- **Overall Median Age (range):** 59.5 years (29 to 75 years)
- **Sex:** 83 (52.5%) male, 75 (47.5%) female
- **Race and Ethnicity:** All participants were Asian (Chinese)
- **ECOG Performance Score:** 69 (43.7%) 0, 89 (56.3%) 1
- **Site of Origin:** 31 (19.6%) gallbladder, 105 (66.5%) intrahepatic, 22 (13.9%) extrahepatic

Efficacy:

The efficacy results of the China subpopulation are generally consistent with the global population.

Primary Endpoint

- In the China subpopulation, pembrolizumab in combination with chemotherapy provided a therapeutic benefit to participants with advanced BTC as shown by a clinically meaningful improvement in OS compared with placebo plus chemotherapy.
    - Treatment with pembrolizumab plus chemotherapy was associated with a clinically meaningful improvement in OS compared with placebo plus chemotherapy (HR 0.74 [95% CI: 0.51, 1.08]). The median OS was 14.1 months (95% CI: 10.4, 17.7) in the pembrolizumab plus chemotherapy group and 9.9 months (95% CI: 8.6, 13.0) in the placebo plus chemotherapy group.
    - The KM curves for OS showed separation 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 (54.7% vs 42.2% at 12 months and 28.0% vs 18.8% at 24 months).

Secondary Endpoints

- There was a favorable trend in PFS in the pembrolizumab plus chemotherapy group when compared with placebo plus chemotherapy based on BICR assessment per RECIST 1.1. The HR was 0.83 (95% CI: 0.58, 1.19).

- The median PFS was 5.6 months (95% CI: 3.2, 7.4) in the pembrolizumab plus chemotherapy group and 5.7 months (95% CI: 4.4, 6.9) in the placebo plus chemotherapy group.

- Although the estimate of the median PFS in the pembrolizumab plus chemotherapy group was similar with the estimate of the median PFS in the placebo plus chemotherapy group, a greater separation of the KM curves was observed at later timepoints and maintained through this study.

- 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 (23.1% vs 14.3% at 12 months and 14.1% vs 9.5% at 18 months).

- Treatment with pembrolizumab plus chemotherapy was associated with a clinically meaningful improvement in ORR when compared with chemotherapy alone based on BICR assessment per RECIST 1.1. The confirmed ORR was 36.0% (95% CI: 25.2, 47.9) with pembrolizumab plus chemotherapy and 28.9% (95% CI: 19.5, 39.9) with placebo plus chemotherapy. Between-treatment difference was 7.1% (95% CI: -7.5, 21.6). A higher proportion of participants achieved a CR in the pembrolizumab plus chemotherapy group than in the placebo plus chemotherapy group (5.3% vs 1.2%).

- Among responders in the China subpopulation, the DOR was longer in the pembrolizumab plus chemotherapy group with a median of 10.2 months (range 1.2+ to 20.6 months) compared with 5.7 months (1.4+ to 18.2 months) in the placebo plus chemotherapy group.

Safety:

- In the China subpopulation, the safety profile 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).

- In the China subpopulation, 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 AEs, SAEs, deaths).

- In the China subpopulation, the incidence of deaths in the study due to AEs was similar between the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups.

- In the China subpopulation, the incidence of treatment discontinuation due to AEs was generally similar between the 2 intervention groups.

- In the China subpopulation, the observed toxicities were generally manageable with standard medical care, drug discontinuation/interruption, and/or corticosteroid use for pembrolizumab AEOSI as appropriate.

- In the China subpopulation, 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/or supportive care as appropriate. The nature, management, and outcome of AEOSI between the 2 treatment groups remained unchanged.

- In the China subpopulation, addition of pembrolizumab to chemotherapy did not demonstrate increased risk of viral hepatitis flare in the BTC population with preexisting HBV/HCV.

- In the China subpopulation, the incidence of HECI was generally similar between the 2 intervention groups and the addition of pembrolizumab to chemotherapy did not demonstrate an increased risk of HECI.

- No new safety concerns were identified for pembrolizumab in the China subpopulation.

- The safety profile of pembrolizumab in combination with chemotherapy in the China subpopulation is generally consistent with that in the global population.

Adverse Event Summary
(China APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	74		82	
with one or more adverse events	73	(98.6)	82	(100.0)
with no adverse event	1	(1.4)	0	(0.0)
with drug-related[a] adverse events	73	(98.6)	82	(100.0)
with toxicity grade 3-5 adverse events	57	(77.0)	62	(75.6)
with toxicity grade 3-5 drug-related adverse events	53	(71.6)	58	(70.7)
with serious adverse events	28	(37.8)	29	(35.4)
with serious drug-related adverse events	21	(28.4)	16	(19.5)
who died	1	(1.4)	3	(3.7)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	18	(24.3)	14	(17.1)
discontinued MK-3475/PLACEBO	9	(12.2)	8	(9.8)
discontinued any chemotherapy	14	(18.9)	13	(15.9)
discontinued all drugs	3	(4.1)	7	(8.5)
discontinued any drug due to a drug-related adverse event	16	(21.6)	10	(12.2)
discontinued MK-3475/PLACEBO	7	(9.5)	5	(6.1)
discontinued any chemotherapy	13	(17.6)	9	(11.0)
discontinued all drugs	3	(4.1)	4	(4.9)
discontinued any drug due to a serious adverse event	10	(13.5)	8	(9.8)
discontinued MK-3475/PLACEBO	7	(9.5)	6	(7.3)
discontinued any chemotherapy	8	(10.8)	7	(8.5)
discontinued all drugs	3	(4.1)	5	(6.1)
discontinued any drug due to a serious drug-related adverse event	8	(10.8)	5	(6.1)
discontinued MK-3475/PLACEBO	5	(6.8)	3	(3.7)
discontinued any chemotherapy	7	(9.5)	4	(4.9)
discontinued all drugs	3	(4.1)	2	(2.4)

[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 the China subpopulation, 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 clinically meaningful improvement in OS compared with chemotherapy alone.
- There was a favorable trend in PFS per RECIST 1.1 by BICR in treatment with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.
- Treatment with pembrolizumab plus chemotherapy resulted in a clinically meaningful improvement in ORR when compared with chemotherapy alone based on BICR assessment per RECIST 1.1.
- Treatment with pembrolizumab plus chemotherapy provided responders with an extended DOR compared with the placebo plus chemotherapy group.
- The efficacy results of the China subpopulation are generally consistent with the global population.

Safety

Based on the results from the China subpopulation, the following safety conclusions can be made:

- The safety profile of pembrolizumab, in combination with chemotherapy, is consistent with the known safety profiles of pembrolizumab monotherapy and chemotherapy, 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.
- The safety profile of pembrolizumab in combination with chemotherapy in the China subpopulation is generally consistent with that in the global population.

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
CDE	Center for Drug Evaluation
CI	confidence interval
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CR	complete response
DCO	data cut off
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FA	final analysis
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HECI	hepatic events of clinical interest
HR	hazard ratio
IND	Investigational New Drug
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
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
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.

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REVISED REPORT DATE: Not applicable