09 November 2023
EMA/534959/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0138

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
1L	First-line
ADA	Antidrug antibodies
AE	Adverse event(s)
AEOSI	Adverse events of special interest
ALT	Alanine transaminase
APaT	All Participants as Treated
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
BTC	Biliary tract carcinoma
CCA	Cholangiocarcinoma
CI	Confidence interval
CL	Clearance
CPS	Combined positive score
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cutoff
DDI	Drug-drug interaction
dMMR	Mismatch repair deficient
DOR	Duration of response
EC_{50}	half-maximal effective concentration
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ENSCCA	European Network for the Study of Cholangiocarcinoma
ePRO	Electronic Patient Reported Outcomes
ESMO	European Society for Medical Oncology
E-R	Exposure-response
EU	European Union
FA	Final analysis
FAS	Full analysis set
FDA	Food and Drug Administration
GBC	Gallbladder cancer
GHS	Global Health Status
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HECI	Hepatic events of clinical interest
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRQoL	Health-related Quality of Life
IA1	Interim analysis 1
IFN	Interferon
IgG	Immunoglobulin G
IL-2	Interleukin-2
ITT	Intention-to-treat

Abbreviation	Definition
KM	Kaplan-Meier
LSM	Least squares mean
mAb	Monoclonal antibody
MMS	Microsatellite Stable
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NSCLC	Non–small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death receptor 1
PD-L1 and -L2	Programmed cell death ligands 1 and 2
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported outcomes
PT	Preferred term
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of Life
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RSD	Reference safety data
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
TIL	Tumor-infiltrating lymphocytes
TNBC	Triple negative breast cancer
TNFα	Tumor necrosis factor-α
TTD	Time-to-deterioration
TTR	Time to response
US	United States
WBC	White blood cell count

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 1 June 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include KEYTRUDA in combination with gemcitabine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults, based on final results from study KEYNOTE-966; this is 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. As a consequence, sections 4.1, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 43.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paolo Gasparini Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	1 June 2023
Start of procedure:	17 June 2023
CHMP Rapporteur Assessment Report	11 August 2023
PRAC Rapporteur Assessment Report	16 August 2023
PRAC members comments	23 August 2023
Updated PRAC Rapporteur Assessment Report	24 August 2023
PRAC Outcome	31 August 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 September 2023
Request for supplementary information (RSI)	14 September 2023
PRAC Rapporteur Assessment Report	12 October 2023
CHMP Rapporteur Assessment Report	25 October 2023
PRAC Outcome	26 October 2023
CHMP members comments	30 October 2023
Updated CHMP Rapporteur Assessment Report	3 November 2023
Opinion	9 November 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The biliary tract carcinoma (BTC) comprises a heterogeneous group of malignancies affecting the biliary tree that are distinguished based on the anatomical localisation (gallbladder, intrahepatic, perihilar, and distal/periampullary). Given the rare frequency of these tumours, the different subtypes are generally pooled together although carrying different epidemiology, risk factors, clinical presentation, molecular features, and prognosis (Manne *et al*, 2021)[1].

[1]Manne, A., Woods, E., Tsung, A. and Mittra, A. (2021) 'Biliary tract cancers: treatment updates and future directions in the era of precision medicine and immuno-oncology', Frontiers in Oncology, 11, pp. 1-16. doi: 10.3389/fonc.2021.768009.

State the claimed the therapeutic indication

The initially applied indication was: KEYTRUDA, in combination with gemcitabine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

Epidemiology and risk factors, screening tools/prevention

BTC is rare accounting for <1% of all human malignancies. The incidence ranges from 0.35 cases per 100,000 in high-income countries to 40-fold in endemic parts of Asia and South America. Risk factors vary between subtypes and geographical regions. Primary sclerosing cholangitis, inflammatory bowel disease, gallstones, liver cirrhosis, hepatitis B and C, primary sclerosing cholangitis (PSC), and (in endemic areas) liver fluke infections, are associated with increased risk of BTC. Gallbladder cancer is also associated with obesity and female sex. Recently, diabetes, obesity and use of hormonal contraceptives have been identified as new risk factors for intrahepatic cholangiocarcinoma (Valle *et al.*, 2021)[2] (Rahman *et al.*, 2021)[3].

Guidelines for imaging-based surveillance of patients with PSC are available (Berry *et al*., 2022)[4]. For the other at-risk clinical conditions, screening has not yet been established.

Risk factors for BTC vary between regions depending on the prevailing etiopathogenesis. However, chronic inflammation of the biliary epithelium is a key feature characterising the different subtypes (Lazcano-Ponce *et al*., 2001)[5].

Clinical presentation, diagnosis and stage/prognosis

Diffuse symptomatology and high-risk invasive diagnostics make biliary tract cancer challenging to diagnose and tumours are often advanced at diagnosis, contributing to the poor overall 5-year relative survival of only 14-16%. Despite variations in geographic distribution and risk factors, the approach to diagnosis and treatment remains the same. The majority of patients are diagnosed in advanced stage and are treated with systemic therapy. Patients presenting with earlier stage disease may undergo curative surgical resection; however, postoperative recurrence is reported in more than half of the patients. Overall, most patients are treated with systemic therapy and prognosis remains poor highlighting the unmet medical need for this condition (Kang *et al.,* 2022)[6].

Management

Chemotherapy has long been the SoC for first-line treatment of advanced BTC, and the cisplatin – gemcitabine doublet is the most commonly adopted therapy in the advanced stage of cancer, with a demonstrated survival advantage compared to gemcitabine alone. Oxaliplatin may be substituted for cisplatin in case of kidney disease, and gemcitabine monotherapy may be preferred in patients with poor

[2] Valle, J.W., Kelley, R.K., Nervi, B., Oh, D.Y. and Zhu, A.X. (2021) 'Biliary tract cancer', Lancet, 397(10269), 428-44. https://doi.org/10.1016/S0140-6736(20)32167-7
[3] Rahman, R., Ludvigsson, J.F., von Seth, E., Lagergren, J., Bergquist, A. and Radkiewicz, C., 2021. Age trends in biliary tract cancer incidence by anatomical subtype: A Swedish cohort study. Cancer Epidemiology, 70, p.101855.
[4] Berry PA, Kotha S. Surveillance imaging in primary sclerosing cholangitis (PSC): evidence, patient preference and physician autonomy. Transl Gastroenterol Hepatol. 2022 Oct 25;7:43. doi: 10.21037/tgh-21-87. PMID: 36300155; PMCID: PMC9468984.
[5] Lazcano-Ponce, E.C., Miquel, J.F., Muñoz, N., Herrero, R., Ferrecio, C., Wistuba, I.I., Alonso de Ruiz, P., Aristi Urista, G. and Nervi, F. (2001) 'Epidemiology and molecular pathology of gallbladder cancer', CA: A Cancer Journal for Clinicians, 51(6), 349-364. https://doi.org/10.3322/canjclin.51.6.349
[6] Kang MJ, Lim J, Han SS, Park HM, Kim SW, Lee WJ, Woo SM, Kim TH, Won YJ, Park SJ. Distinct prognosis of biliary tract cancer according to tumor location, stage, and treatment: a population-based study. Sci Rep. 2022 Jun 17;12(1):10206. doi: 10.1038/s41598-022-13605-3. PMID: 35715440; PMCID: PMC9205970.

clinical performance (i.e. PS of 2 or other factors of fragility). The recently concluded TOPAZ-1 study provided evidence for improvement in OS with the immune checkpoint inhibitor durvalumab in addition to cisplatin-gemcitabine compared to chemotherapy alone. This combination has been included in the most up-to-date clinical guidance as recommended first-line treatment for advanced BTC (ESMO 2023)[7]. Alternative therapeutic schemes, including triplet regimens, are currently under investigation.

2.1.2. About the product

Pembrolizumab is a humanised mAb which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Since its first approval within Europe for the treatment of advanced melanoma in 2015, pembrolizumab has been licensed for a number of different malignancies, both as monotherapy or in association to chemotherapy.

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No Scientific Advice was sought by the EMA during the development program of pembrolizumab for the BTC indication.

2.1.4. General comments on compliance with GCP

The MAH claimed that the clinical studies were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. All studies were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

[7] ESMO Congress 2023 (2023) Madrid, Spain, 20-24 October 2023. Available at: https://www.esmo.org/meeting-calendar/esmo-congress-2023 (Accessed: 26 October 2023). Valle, J.W., Kelley, R.K., Nervi, B., Oh, D.-Y. and Zhu, A.X. (2021) 'Biliary tract cancer', The Lancet, 397(10272), pp. 428–444. doi: 10.1016/S0140-6736(21)00153-7

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number/Status	**Design**	**Population**	**Dosage, Regimen**	**Primary Efficacy Endpoint**
KEYNOTE-966 Ongoing	Randomized, double-blind, placebo-controlled, parallel group, multisite	Participants with advanced/unresectable biliary carcinoma (intrahepatic, extrahepatic, or gallbladder, excluding ampulla of vater cancers)	Arm A: pembrolizumab 200 mg Q3W + gemcitabine 1000 mg/m^2 + cisplatin 25 mg/m^2 on Day 1 and 8 of each cycle Arm B: placebo + gemcitabine 1000 mg/m^2 + cisplatin 25 mg/m^2 on Day 1 and 8 of each cycle	OS
OS=overall survival; Q3W=once every 3 weeks.				

2.3.2. Pharmacokinetics

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

PK data form study KEYNOTE-966 were used in support of 200 mg Q3W as the recommended dose of pembrolizumab in combination with chemotherapy in participants with advanced BTC.

Substantial characterization of the PK and immunogenicity of pembrolizumab have been provided in previous submissions. In particular, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled on KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the USPI and EU SmPC.

In addition to the dosing regimens of 200 mg Q3W or 2 mg/kg Q3W, the 400 mg Q6W dosing regimen was also approved in the EU for all adult monotherapy indications (procedure number EMEA/H/C/003820/II/0062) and for all adult indications in combination with other anticancer agents (procedure number EMEA/H/C/003820/II/0102).

Absorption

Pembrolizumab is dosed via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Elimination

Pembrolizumab clearance (CL) is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]). The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic target population

Considering that an extensive characterization of the PK and immunogenicity profile of pembrolizumab have been provided in previous submissions, in this submission the focus is on the data related to the characterization of the pharmacology for the combination of pembrolizumab with chemotherapy (gemcitabine 1000 mg/m2 + cisplatin 25 mg/m2) in participants with advanced BTC.

PK Data KEYNOTE-966

KEYNOTE-966 is a randomized, double-blind, placebo-controlled, parallel group, multisite, Phase 3 study, designed to evaluate the efficacy and safety of pembrolizumab plus chemotherapy (gemcitabine and cisplatin) in participants with previously untreated advanced BTC.

PK Analysis Pembrolizumab

The objectives of the PK analysis were:

- To evaluate pembrolizumab concentrations obtained from subjects in the study of KEYNOTE-966.
- To compare pembrolizumab PK data in KEYNOTE-966 observed in the pembrolizumab plus gemcitabine/cisplatin treatment arm with reference (TDPK) model-predicted pembrolizumab PK.
- To compare KEYNOTE-966 observed pembrolizumab PK data with historical monotherapy data.

Table 1 Overview of cohorts included in KEYNOTE-966 pembrolizumab PK analysis

Study/Cohort	Cancer Type	Treatment	Number of subjects providing PK[a]
KEYNOTE-966 Global Study	Biliary tract carcinoma	Pembrolizumab (200 mg Q3W) plus gemcitabine/cisplatin	523
a Unique subjects providing an evaluable PK sample; Q3W = Every 3 weeks.			

PK sampling schedule in KEYNOTE-966 for pembrolizumab: pre-infusion pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycle 1, 2, 4 and 8 and every 4 cycles thereafter. Post-dose samples (Cmax) were drawn at Cycle 1 and 8, approximately 30 minutes after the end of pembrolizumab infusion.

Phoenix™ WinNonlin® (Version 8.1.1.279) software was used for pharmacokinetic analysis.

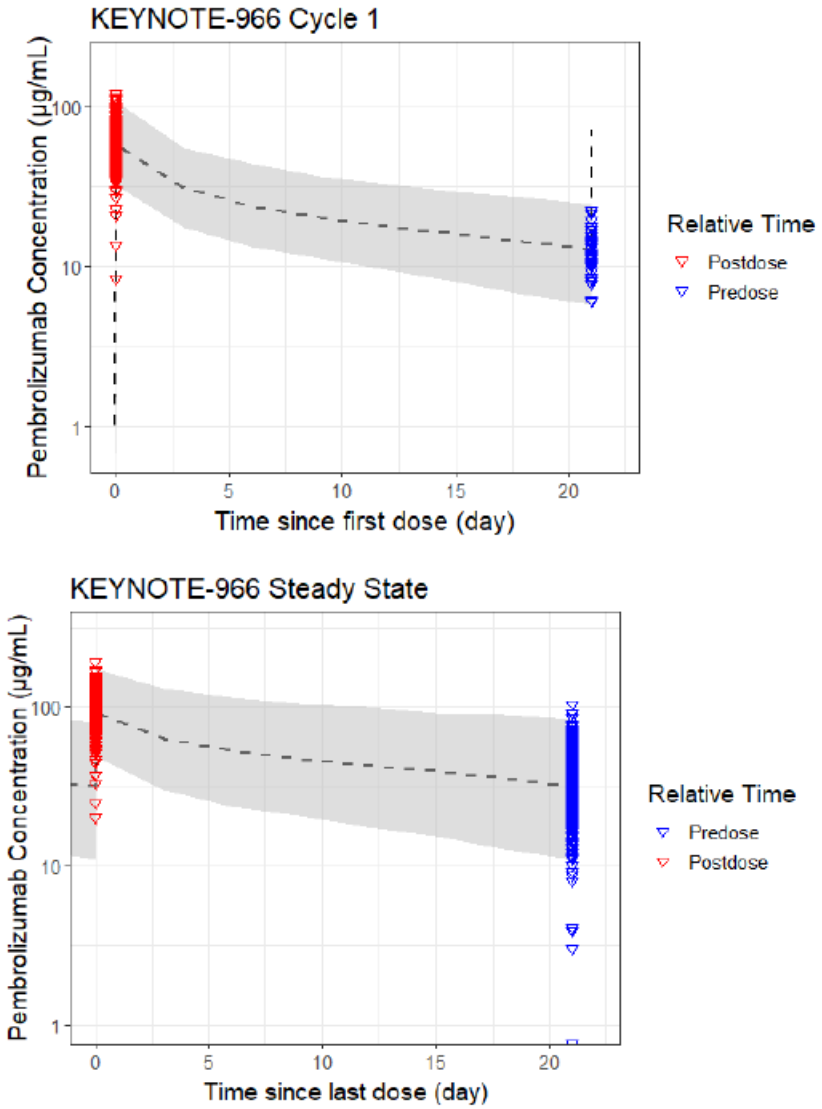
Summary descriptive statistics of the pre-dose and post-dose concentrations by cycle are presented in the following table:

Table 2 Summary statistics of pembrolizumab predose (Ctrough) and postdose (Cmax) serum concentration values from the treatment arm of pembrolizumab plus gemcitabine/cisplatin following administration of multiple I.V. doses of 200 mg Q3W pembrolizumab in KEYNOTE-966

Cycle	NOMTAFD (day)	N	GM (%CV)	AM (SD)	Min	Median	Max
			(µg/mL)				
Predose (C_{trough})							
Cycle 1 (Week 0)	0.00	496	-	0.00 (0.0)	0.00	0.00	0.00
Cycle 2 (Week 3)	21.0	49	12.2 (33.4)	12.8 (4.0)	5.04	12.0	22.4
Cycle 4 (Week 9)	63.0	38	22.6 (32.0)	23.7 (6.9)	10.5	24.1	39.8
Cycle 8 (Week 21)	147	269	-	36.2 (12.8)	0.00	36.0	90.9
Cycle 12 (Week 33)	231	182	-	37.2 (14.9)	0.00	36.5	92.6
Cycle 16 (Week 45)	315	96	35.5 (53.9)	39.3 (16.3)	3.01	37.2	91.7
Cycle 20 (Week 57)	399	48	38.2 (41.9)	41.1 (15.4)	11.7	38.8	86.2
Cycle 24 (Week 69)	483	29	35.2 (78.5)	42.3 (22.7)	4.21	39.3	104
Cycle 28 (Week 81)	567	15	35.7 (57.0)	39.6 (15.2)	9.79	44.0	65.6
Cycle 32 (Week 93)	651	10	36.2 (54.4)	40.1 (17.8)	11.7	36.3	77.7
Postdose (C_{max})							
Cycle 1 (Week 0)	0.021	483	60.3 (28.8)	62.5 (16.0)	8.37	62.2	120
Cycle 8 (Week 21)	147	268	91.6 (31.5)	95.7 (27.1)	20.1	92.3	192
AM = Arithmetic Mean; CV% = Geometric Coefficient of Variation; GM = Geometric Mean; Min = Minimum; Max = Maximum; NOMTAFD = Nominal time after first administration; SD = Standard Deviation; Results reported for time points with N ≥ 3.							

Observed pembrolizumab concentration data in KEYNOTE-966 for pembrolizumab plus chemotherapy group are overlaid on the simulated profile using the reference PK model as shown in Figure 1.

Figure 1 Observed pembrolizumab concentration data in KEYNOTE-966 from the treatment arm of pembrolizumab plus gemcitabine/cisplatin receiving 200 mg Q3W with reference model-predicted pharmacokinetic profile for 200 mg Q3W dose regimen at Cycle 1 and Steady state (at and after Cycle 8), Global study



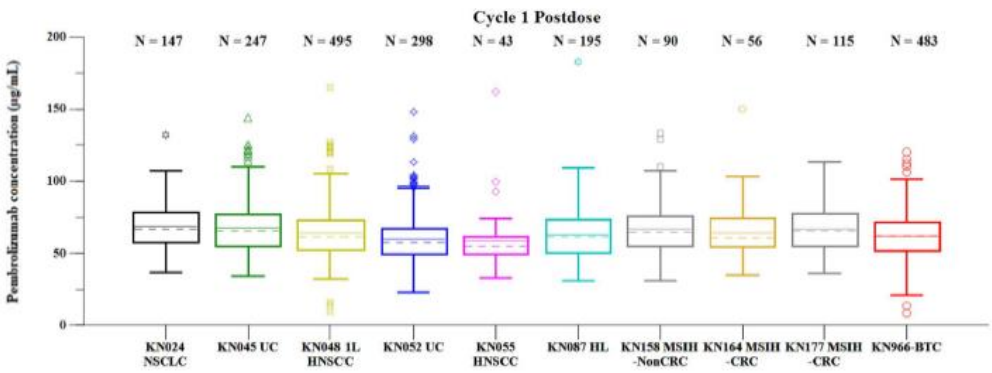
Tabular summaries of descriptive statistics and boxplots from early drug treatment at Cycle 1 end of infusion (post-dose) and at pre-dose Cycle 2 and Cycle 8, comparing observed pembrolizumab concentrations of 200 mg (Q3W) from participants with advanced BTC in KEYNOTE-966 and monotherapy trials in non-small cell lung cancer (NSCLC, KEYNOTE-024), urothelial cancer (UC, KEYNOTE-045 and KEYNOTE- 052), head and neck squamous cell cancer (HNSCC, KEYNOTE-048 and KEYNOTE-055), classical Hodgkin Lymphoma (HL, KEYNOTE-087), microsatellite instability-high cancer (MSI-H, KEYNOTE-158) and MSI-H colorectal cancer (MSI-H-CRC, KEYNOTE-164 and KEYNOTE-177), are presented in Table 3 and Figure 2 reported below.

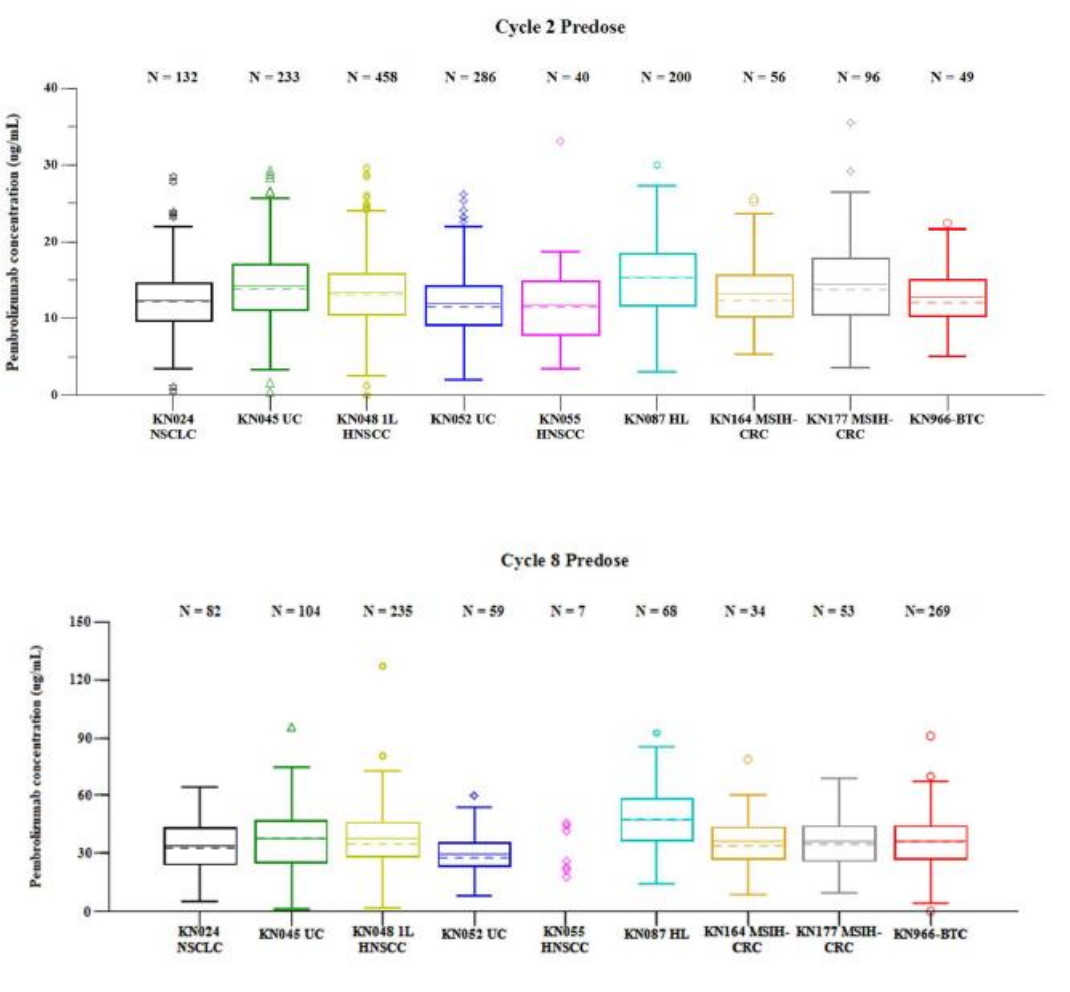
Table 3 Summary statistics of observed pembrolizumab concentrations at Cycle 1 postdose, Cycle 2 and Cycle 8 predose in various monotherapy trials (KEYNOTE-024, -045, -048, -052, -055, -087, 158 MSIH non CRC, -164, -177) and KEYNOTE-966 advanced/unresectable biliary tract carcinoma

Time point	Dose (mg)	Study / Indication	N	GM(CV%) (µg/mL)	AM(SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 1 Postdose	200	KN024 NSCLC	147	67.5 (23.1)	69.3 (16.2)	36.6	66.8	132
	200	KN045 UC	247	65.7 (26.2)	67.9 (18.2)	33.9	65.9	144
	200	KN048 1L HNSCC	495	61.8 (28.7)	64.2 (17.6)	9.48	61.7	165
	200	KN052 UC	298	58.0 (27.9)	60.2 (17.3)	22.8	57.4	148
	200	KN055 HNSCC	43	56.5 (27.8)	58.9 (20.7)	33.1	54.9	162
	200	KN087 HL	195	60.7 (28.0)	63.1 (18.3)	31.2	61.3	183
	200	KN158 MSIH-NonCRC	90	64.4 (27.0)	66.7 (18.3)	31.2	65.2	133
	200	KN164 MSIH-CRC	56	62.2 (27.8)	64.6 (19.1)	34.9	61.2	150
	200	KN177 MSIH-CRC	115	65.0 (25.7)	67.1 (17.1)	36.4	65.7	113
	200	KN966-BTC	483	60.3 (28.8)	62.5 (16)	8.37	62.2	120
Cycle 2 Predose	200	KN024 NSCLC	132	11.1 (54.1)	12.3 (4.7)	0.535	12.2	28.5
	200	KN045 UC	233	13.1 (47.2)	14.2 (4.9)	0.475	13.9	29.3
	200	KN048 1L HNSCC	458	-	13.4 (4.6)	0.00	13.2	29.6
	200	KN052 UC	286	11.1 (42.3)	11.9 (4.4)	2.07	11.5	26.2
	200	KN055 HNSCC	40	10.7 (47.2)	11.8 (5.2)	3.45	11.6	33.1
	200	KN087 HL	200	14.4 (39.5)	15.4 (5.1)	3.06	15.3	30.0
	200	KN164 MSIH-CRC	56	12.5 (35.3)	13.2 (4.6)	5.44	12.4	25.6
	200	KN177 MSIH-CRC	96	13.2 (45.7)	14.4 (5.9)	3.64	13.9	35.5
	200	KN966- BTC	49	12.2 (33.4)	12.8 (4)	5.04	12.0	22.4
Cycle 8 Predose	200	KN024 NSCLC	82	30.6 (49.6)	33.6 (13.3)	5.26	32.7	64.1
	200	KN045 UC	104	33.4 (63.7)	37.8 (16.5)	1.13	37.5	95.6
	200	KN048 1L HNSCC	235	34.2 (50.3)	37.5 (15.1)	1.77	34.8	127
	200	KN052 UC	59	28.0 (38.4)	29.9 (10.4)	8.15	27.9	59.8
	200	KN055 HNSCC	7	27.8 (41.0)	29.6 (11.4)	16.8	24.5	43.3
	200	KN087 HL	68	43.9 (43.5)	47.4 (17)	13.9	47.5	92.4
	200	KN164 MSIH-CRC	34	33.6 (43.1)	36.2 (13.8)	8.40	33.7	78.8
	200	KN177 MSIH-CRC	53	32.9 (49.2)	36.2 (15.1)	9.76	34.7	68.5
	200	KN966- BTC	269	-	36.2 (12.8)	0.00	36.0	90.9

GM = Geometric Mean; %CV = Geometric Coefficient of Variation; AM = Arithmetic Mean; SD = Standard Deviation; NSCLC = non-small cell lung cancer; UC = urothelial cancer; HNSCC = head and neck squamous cell carcinoma; HL = Hodgkin lymphoma; MSIH CRC= micro satellite instability high cancer colorectal cancer; BTC = Biliary tract carcinoma.

Figure 2 Pembrolizumab observed concentrations at Cycle 1 postdose, Cycle 2 and Cycle 8 predose in various monotherapy trials (KEYNOTE-024, -045, -048, -052, -055 -087, 158 MSIH non CRC, -164, -177) and KEYNOTE-966





2.3.3. Pharmacodynamics

Mechanism of action

Keytruda is an antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Keytruda potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Primary and secondary pharmacology

Immunogenicity

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment ADA across different pembrolizumab regimens (1.4 – 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated impact on efficacy or safety, as currently

summarized in the EU SmPC and USPI. This low rate of immunogenicity has been shown to be consistent across tumour type and no clinically meaningful consequences have been observed in the subjects with a positive immunogenicity reading. Additionally, incidence of ADA has not been impacted by the presence of another small molecule or chemotherapy in combination with pembrolizumab.

2.3.4. PK/PD modelling

No new information regarding PK/PD modelling for pembrolizumab is available within this application.

2.3.5. Discussion on clinical pharmacology

In this application, the focus is on PK data related to the combination of pembrolizumab with chemotherapy (gemcitabine/cisplatin) from study KEYNOTE-966.

Absorption

The dosing regimen of 400 mg Q6W is applicable across all adult indications regardless of the combination treatment type, thus, the 400 mg Q6W dosing regimen would have a similar benefit-risk profile as the 200 mg Q3W (or 2 mg/kg Q3W) dosing regimen in the clinical use of pembrolizumab in participants with BTC.

Elimination

Pembrolizumab clearance (CL) is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic

PK data from KEYNOTE-966 show that the observed pembrolizumab serum concentration values in subjects with advanced BTC are contained within the 90% CI of the reference PK model, which indicate consistency with the historical data, in both Cycle 1 postdose and Cycle 8 predose (at steady state).

In addition, tabular summaries of descriptive statistics and boxplots from early drug treatment at Cycle 1 end of infusion (post-dose) and at pre-dose Cycle 2 and Cycle 8 show that observed pembrolizumab concentrations of 200 mg (Q3W) in combination with chemotherapy (gemcitabine/cisplatin) from participants with advanced BTC in KEYNOTE-966 are similar to the observed pembrolizumab concentration when administered as monotherapy in other trials in different cancer indications.

No new data on immunogenicity have been submitted within this application and this is acceptable considering that the incidence of antidrug antibodies (ADA) has been already evaluated in the presence of chemotherapy in combination with pembrolizumab.

In conclusion, pembrolizumab PK disposition is not affected by the co-administration with chemotherapy, in particular by the co-administration of gemcitabine plus cisplatin.

2.3.6. Conclusions on clinical pharmacology

Pembrolizumab PK disposition is not affected by the co-administration with chemotherapy (gemcitabine plus cisplatin) for advanced BTC. Observed concentrations from KEYNOTE-966 overlaid on the reference

model predicted median concentrations both at Cycle 1 and at steady state and are consistent with other globally approved studies in different cancer indications.

2.4. Clinical efficacy

The current submission is based on a single pivotal study (KEYNOTE-966).

This is a randomised, 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).

The report is based on the final analysis (FA data cut-off date 15-DEC-2022).

2.4.1. Dose response study(ies)

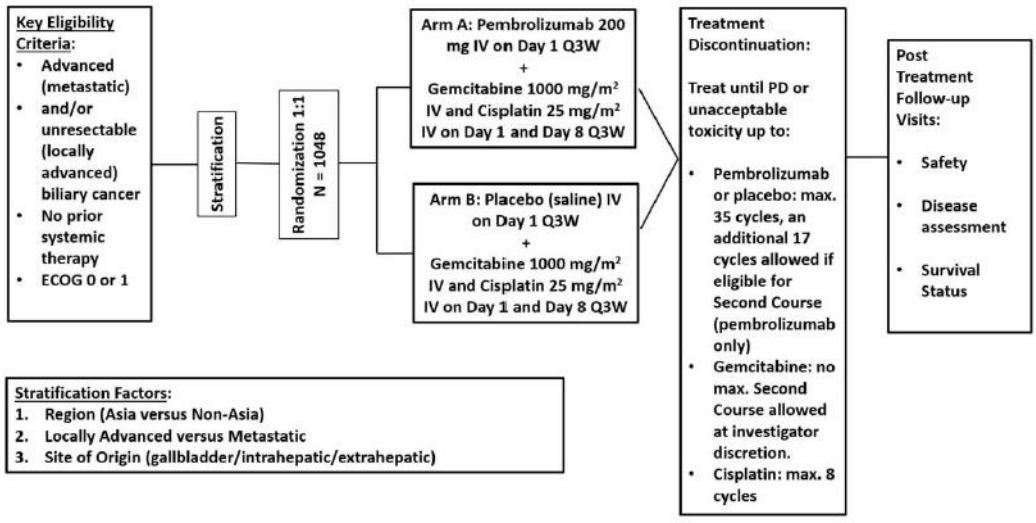
No dose-response studies were submitted as part of this application.

2.4.2. Main study

Title of Study

KEYNOTE-966: 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

Figure 3 KEYNOTE-966 Study design



ECOG=Eastern Cooperative Oncology Group; IV=intravenous; max=maximum; N=number of participants; PD=progressive disease; Q3W=every 3 weeks.

Methods

Study participants

Inclusion criteria

Participants were eligible for inclusion in the study if they met all of the following key inclusion criteria:

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

2. Had measurable disease based on RECIST 1.1, as determined by the site investigator.

3. Participants with past or ongoing HCV infection were eligible for the study. Treated participants must have completed their treatment at least 1 month prior to starting study intervention. Untreated or incompletely treated HCV participants could have initiated antiviral therapy for HCV if liver function remained stable for at least 3 months on study intervention.

4. Participants with controlled HBV infection were eligible if they met the following criteria:

- Participants with chronic HBV infection, defined as HBsAg positive and/or detectable HBV DNA, must have been given antiviral therapy for HBV for at least 4 weeks prior to the first dose of study intervention and HBV viral load must have been less than 100 IU/mL prior to first dose of study intervention. Participants on active HBV therapy with viral loads under 100 IU/mL were to stay on the same therapy throughout study intervention. Antiviral therapy after completion of study intervention was to follow local guidelines.

- Participants with clinically resolved HBV infection, defined as HBsAg negative and anti-HBc positive, and who had an undetectable HBV viral load at screening were to be checked Q6W for HBV viral load and treated for HBV if viral load was over 100 IU/mL. Antiviral therapy after completion of study intervention was to follow local guidelines.

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

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

7. Had a life expectancy of greater than 3 months.

8. Patients were required to have adequate organ function as defined in the following table:

Table 4 Inclusion criteria KEYNOTE-966: organ function requirements

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 (GFR can also be used in place of creatinine or CrCl)	≤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); GFR=glomerular filtration rate; ULN=upper limit of normal.
[a]Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.
[b]Creatinine clearance (CrCl) should be calculated using the Cockcroft-Gault Method: Refer to Appendix 10 for appropriate calculation.
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.

Exclusion criteria

Participants were excluded from the study if they met one of the following key exclusion criteria:

1. Had previous systemic therapy for advanced (metastatic) or unresectable (locally advanced) BTC (intra-or extra hepatic cholangiocarcinoma or gallbladder cancer), with the exception of neoadjuvant/adjuvant therapy which was 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 were excluded.

2. Had ampullary cancer.

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

4. Had an active autoimmune disease that required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

5. Had 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).

6. Had received prior anticancer therapy (e.g., 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.

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

Treatments

Table 5 Study interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	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 administrations	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 administrations	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

Definitions of IMP and NIMP are 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) of the study protocol [16.1.1] for country-specific requirements.

IMP=Investigational Medicinal Product; IV=intravenous; N/A=Not applicable; NIMP=Non-Investigational Medicinal Product; PD=progressive disease.

Objectives/endpoints

Table 6 Objectives and endpoints

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)
• 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

Objectives	Endpoints
• 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 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

Sample size

Approximately 1048 participants were expected to be randomized 1:1 into pembrolizumab plus gemcitabine plus cisplatin or placebo plus gemcitabine plus cisplatin. After enrollment of the global portion was complete, the study remained open to enrolment in China alone for the China extension cohort of 46 participants until a total of 158 participants had been enrolled across the global and extension parts to meet local regulatory requirements in China. This report describes the global portion of the study. OS was the sole primary endpoint for the study, with PFS and ORR as the key secondary endpoints. The working model in evaluating the power of both OS and PFS analyses and projecting event accumulation with time assumed that both OS and PFS had an approximately 2-month delay in treatment effect.

Specifically, the model assumed that the OS curves for the pembrolizumab plus gemcitabine/cisplatin arm and placebo plus gemcitabine/cisplatin arm coincided over the first 2 months with HR=1 and diverged when the treatment effect with constant HR=0.75 starts at 2 months. Based on a 11-month control median, under the delayed treatment effect model, the median of the pembrolizumab plus gemcitabine/cisplatin arm was estimated approximately 14.0 months (~3-month increment). For the OS endpoint, based on a target number of 818 events and 2 interim analyses, assuming HR=1 for the first 2 months and HR=0.75 after 2 months, the study had approximately 93% power to reject the null hypothesis under the alternative hypothesis at an overall alpha level of 0.025 (1-sided).

Regarding the PFS curves, the model assumes that for the pembrolizumab plus gemcitabine/cisplatin arm and placebo plus gemcitabine/cisplatin arm coincided over the first 2 months with HR=1 and diverge when the treatment effect with constant HR=0.7 starts at 2 months. Based on a 6-month control median, under the delayed treatment effect model, the median of pembrolizumab plus gemcitabine/cisplatin arm was estimated approximately 7.7 months (~1.6-month increment). For the PFS endpoint, if OS endpoint was successful, based on the expected number of 786 events at PFS final analysis, assuming HR=1 for the first 2 months and HR=0.7 after 2 months, the study had approximately 92% power to reject the null hypothesis under the alternative hypothesis at an overall alpha level of 0.0125 (1-sided).

The sample size and power calculations for PFS and OS assumed the following: 1) PFS follows an exponential distribution with a median of 6 months for the control group; HR=1 for the first 2 months and HR=0.7 after 2 months; 2) OS follows an exponential distribution with a median of 11 months for the control group; HR=1 for the first 2 months and HR=0.75 after 2 months; 3) Enrollment period of 20 months with a ramp-up period of 6 months; 4) A monthly drop-out rate of 2% and 0.1% for PFS and OS, respectively; 5) The interim and final analyses were planned at ~26, ~32 and ~38 months after the start of randomization and the minimum alpha spending approach is employed.

If OS endpoint was successful, the ORR power calculation was based on the following assumptions: 1) under an overall alpha level of 0.0125; 2) the underlying ORR was 25% in the placebo +gemcitabine/cisplatin arm. The study had ~91% power to detect a true ORR rate difference of 10% (pembrolizumab + gemcitabine/cisplatin versus placebo +gemcitabine/cisplatin).

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

Randomisation

Treatment allocation/randomization occurred centrally using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants were randomized in a 1:1 ratio to receive either pembrolizumab or placebo each in combination with chemotherapy. Treatment randomization was stratified based on the following criteria:

1) Region (Asia versus non-Asia);

2) Locally Advanced versus Metastatic (in the event the participant has locally advanced and metastatic BTC, the participant should be stratified as metastatic);

3) Site of Origin (gallbladder, intrahepatic, or extrahepatic).

Blinding (masking)

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.

As of the data cutoff for the FA, a total of 31 participants were prematurely unblinded as emergency unblindings and 1 of those emergency unblindings was inadvertent. A total of 62 nonemergency unblindings occurred for purposes of selection of subsequent therapy. Nonemergency unblindings required SCF approval and all critical data to be entered to decrease risk of bias. A total of 4 second course unblindings occurred to determine second course eligibility. Second course unblinding required centrally verified disease progression. The premature unblinding of these participants did not have a major impact on study conduct or on the outcome of the study, and none of these premature unblindings led to exclusion from the analysis. These unblinding events were reviewed via the Sponsor's Significant Quality Issues process and were determined to have no impact on the quality of the data.

Statistical methods

Protocol Amendments involving statistical methods

The protocol was subject to six general amendments, of which Amendment 2 (08-DEC-2020), Amendment 4 (26-AUG-2021) and Amendment 5 (18-NOV-2021) modified the statistical analysis plan (SAP) language as follows. Statistical methods were reported in the protocol section and in the Amendment 04 of supplemental SAP (sSAP) dated 13-JUN-2022.

Amendment 2 (08-DEC-2020): The protocol was revised to make OS the sole primary endpoint and to change PFS from a primary to a secondary endpoint. A more conservative hazard ratio assumption for OS was made accounting for possible delayed treatment effect; as consequence the sample size was increased from initial 788 to 1048 participants, to maintain study timelines and statistical power. The futility analysis was removed since early results are not informative in the presence of a delayed treatment effect. The interim and final analyses timing was updated from calendar-based to event-based and the multiple strategy was also updated to allocate all initial alpha to OS as a single primary endpoint and split the alpha equally between ORR and PFS when OS demonstrated superiority. Two interim analyses (IAs) were planned at ~500 OS events (~29 months) and ~616 OS events (~35 months), respectively. The FA was planned after the occurring of ~725 OS events (~41 moths from the start of randomization).

Amendment 4 (26-AUG-2021): The SAP was updated to account 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. The first IA was removed and the number of OS events at each analysis was increased. The IA was planned after ~695 OS events (~32 months) and the FA was planned after ~818 OS events (~38 months). The analyses were triggered by required time and OS events, the minimum alpha spending approach for OS analysis was used and the group-sequential analysis of PFS and ORR was changed to a single analysis at the time of OS interim analysis.

Amendment 5 (18-NOV-2021): A new, earlier interim analysis (IA1) for OS was added to take into account the emerging external data showing positive results for immunotherapy plus chemotherapy as first-line therapy for patients with advanced biliary tract carcinoma. The IA1 was planned at ~585 OS events (~26 months), the IA2 was planned at ~695 OS events (~32 months) and the FA was planned after ~818 OS events (~38 months).

Additional details on protocol amendments can be found under "conduct of the study" below.

Interim analysis

Two interim analyses (IA) were planned in addition to the final analysis (FA) for this study. The efficacy analyses in this submission are based on FA. The timing and the purpose of each analysis are summarized in the table below.

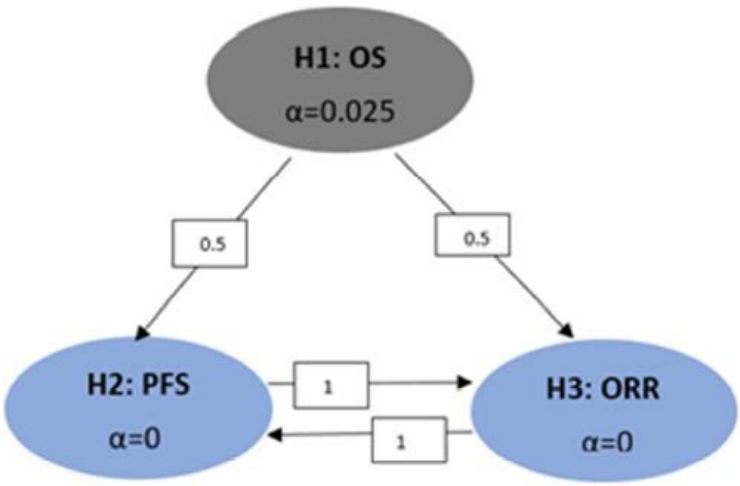
Table 7 KEYNOTE-966: Purpose of Interim Analyses and Final Analysis

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: IA1=interim analysis 1; IA2=interim analysis 2; FA=final analysis; OS=overall survival.			

Type I error and multiplicity control

The trial used the graphical method of Maurer and Bretz to control 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 below shows the multiplicity diagram for type I error control.

Figure 4 KEYNOTE-966: Multiplicity diagram for Type I error control



Initial one-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others were represented in the boxes on the lines connecting

hypotheses. The initial α assigned to OS will be 0.025. If OS hypothesis was rejected, the corresponding alpha was reallocated equally to PFS and ORR. If the PFS hypothesis was rejected, the corresponding alpha was reallocated to ORR. If the ORR hypothesis was rejected, the corresponding alpha was reallocated to PFS. Within each endpoint, the Type I error control across the interim and final analyses has been maintained by the use of the Lan-DeMets spending function approach with O'Brien-Fleming boundaries.

OS

The initial α-level for testing OS is 0.025. Under the alternative hypothesis, the treatment effect were delayed by 2 months, with OS HR=1 in the first 2 months, and HR=0.75 after 2 months. Table below shows the boundary properties for OS hypothesis testing based on the minimum alpha spending strategy using a Lan-DeMets spending function approximating O'Brien-Fleming boundaries.

Table 8 KEYNOTE-966: Boundary properties for OS hypothesis testing based on the minimum alpha spending strategy

Analysis	Value	α = 0.025
IA1 : 72%* N: 1069 Events: 585 Month: ~26	Z	2.4072
	p (1-sided)[a]	0.0080
	HR at bound[b]	0.8199
	P(Cross) if HR = 1[c]	0.0080
	P(Cross) under the alternative hypothesis[d,e]	0.6170
IA2 : 85%* N: 1069 Events: 695 Month: ~32	Z	2.2409
	p (1-sided)[a]	0.0125
	HR at bound[b]	0.8451
	P(Cross) if HR = 1[c]	0.0150
	P(Cross) under the alternative hypothesis[d,e]	0.8154
FA N: 1069 Events: 818 Month: ~38	Z	2.0438
	p (1-sided)[a]	0.0205
	HR at bound[b]	0.8669
	P(Cross) if HR = 1[c]	0.0250
	P(Cross) under the alternative hypothesis[d,e]	0.9266

Abbreviations: HR=hazard ratio; IA1=interim analysis 1; IA2=interim analysis 2; FA=final analysis.
The number of events is approximate.
* Percentage of total planned events at the interim analysis.
[a] The nominal α for testing.
[b] The approximate HR required to reach an efficacy bound.
[c] P(Cross if HR = 1) is the cumulative probability of crossing a bound under the null hypothesis.
[d] The alternative hypothesis is HR=1 for the first 2 months and HR=0.75 after 2 months.
[e] P(Cross) under the alternative hypothesis is the cumulative probability of crossing a bound under the alternative hypothesis; estimated through simulations

The bounds provided were based on the assumption that the number of OS events at IA1, IA2 and FA are 585, 695 and 818, respectively. 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 has been adopted. At an IA, the information fraction

used in Lan-DeMets spending function to determine the alpha spending at the IA was based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically, the information fraction was calculated as the observed number of events at the IA over the target number of events at the FA, if the observed number of events was less than the expected, or as the expected number of events at the IA over the target number of events at FA, if the observed number of events exceeded the expected number. The FA used the remaining Type I error that has not been spent at the earlier analyses. The event counts for all analyses were used to compute the correlations.

PFS

The PFS hypothesis was not allocated any alpha initially and might only be tested when the OS was successful. The study tested PFS at IA1 (final PFS analysis). The p-value based on PFS data observed at IA1 was calculated and compared to its corresponding p-value bound when OS demonstrated superiority and alpha for PFS test became available. At IA2 and FA data cutoff a descriptive analysis of PFS might also be provided when superiority in OS was demonstrated. Following the outlined multiplicity strategy, the PFS hypothesis might be tested at α=0.0125 (if the OS null hypothesis was rejected), or at α=0.025 (if both the OS and ORR null hypotheses were rejected). Under the alternative, the treatment effect was delayed by 2 months, with PFS HR=1 in the first 2 months, and HR=0.7 after 2 months. The boundary properties and power for each of these alpha levels are shown below.

Table 9 KEYNOTE-966: Boundary properties and power for each alpha level (PFS)

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.

ORR

The ORR hypothesis was not allocated any alpha initially and might only be tested when the OS was successful. The study tested ORR at IA1 (final ORR analysis). The p-value based on ORR data observed at IA1 was calculated and compared to its corresponding p-value bound when OS demonstrated superiority and alpha for ORR test becomes available. At IA2 and FA data cutoff a descriptive analysis of ORR might also be provided when superiority in OS was demonstrated. Table below 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.

Table 10 KEYNOTE-966: Boundary properties and power for each alpha level (ORR)

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.

Efficacy analyses

The Intention-to-Treat (ITT) population, which consisted of all 1069 randomized participants, served as the population for primary efficacy analyses. All randomized participants were included in this population. Participants were included in the treatment group to which they were randomized, regardless of whether they received study treatment. The duration of response (DOR) analysis was based on the population of responders (participants that achieved complete or partial response). A summary of the analysis strategy for key efficacy endpoints as well as censoring rules for primary and sensitivity analyses of PFS and DOR are presented in the following tables:

Table 11 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 1]
ORR per RECIST 1.1 by BICR	Testing and estimation: stratified Miettinen and Nurminen method	ITT	Participants with missing response data are considered nonresponders.

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.

†: Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (See Section 3.6.1 for strata collapsing strategy) will be applied to the analysis model.

Table 12 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 the earliest date of 1) last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and 2) the last disease assessment prior to new anticancer therapy, if any. In a special case of participants without post-randomization scans who died later than after ≥2 consecutive missed disease assessments or started new anticancer therapy, the PFS will be censored on the randomization date.	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. In a special case of participants without post-randomization scans, the PFS will be censored on the randomization date.	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 therapy. In a special case of participants without post-randomization scans who started new anticancer therapy, the PFS will be censored on the randomization date.	Censored at last disease assessment	Progressed at date of new anticancer treatment
Abbreviations: PD=progressive disease; PFS=progression-free survival.			

The non-parametric Kaplan-Meier (KM) method was used to estimate the PFS and OS curve in each treatment group. The treatment difference in PFS and OS was assessed by the stratified log-rank test. For PFS and OS a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference between the treatment arms. The hazard ratio (HR) and its 95% confidence interval (CI) from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported. The same stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model. At FA of SOS, a sensitivity analysis based on the MaxCombo test with logrank FH (0, 1), FH (1, 1) might be performed to account for the potential loss of power with logrank test in case of proportional hazard assumption violation. In order

to evaluate the robustness of the PFS endpoint, 2 sensitivity analyses with different sets of censoring rules were performed, as described in the table above.

The stratified Miettinen and Nurminen method with weights proportional to the stratum size was used for the comparison of the ORR between the two treatment groups. The point estimate of ORR was provided by treatment group, together with a 95% CI using the exact binomial method proposed by Clopper and Pearson (1934). The stratification factors used for randomization were applied to the analysis. The descriptive analysis of ORR based on all participants was performed after IA1. No formal hypothesis testing was conducted.

DOR was summarised descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who showed a complete response (CR) or partial response (PR) were included in this analysis. For each DOR analysis, a corresponding summary of the censoring reasons for responding participant were also provided. Responding subjects who were alive, had not progressed, had not initiated new anti-cancer treatment, had not been determined to be lost to follow-up, and had a disease assessment within ~5 months of the data cutoff date were considered ongoing responders at the time of analysis. If a subject met multiple criteria for censoring, the censoring criterion that occurred earliest was applied.

There were 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). The analysis stratification was based on the value of the randomization factor entered into the IVRS. For the purpose of analysis, some of the small strata among the 12 strata formed by the 3 factors were combined to ensure sufficient number of participants and events in each stratum. The stratification cells were pooled to form the following 10 analysis strata that were used in all stratified analyses:

1. Asia and Locally Advanced and [Extrahepatic or Gallbladder]
2. Asia and Locally Advanced and Intrahepatic
3. Asia and Metastatic and Gallbladder
4. Asia and Metastatic and Extrahepatic
5. Asia and Metastatic and Intrahepatic
6. Non-Asia and Locally Advanced and [Extrahepatic or Gallbladder]
7. Non-Asia and Locally Advanced and Intrahepatic
8. Non-Asia and Metastatic and Gallbladder
9. Non-Asia and Metastatic and Extrahepatic
10. Non-Asia and Metastatic and Intrahepatic

Subgroup analyses

Subgroup Analyses and Effect of Baseline Factors were planned. To determine whether the treatment effect was consistent across various subgroups, the between-group treatment effect for OS, PFS, and ORR (with a nominal 95% CI) was 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 radiation (yes, no); Prior chemotherapy (yes, no); Prior PDT (yes, no); Smoking status (never, former, current); Microsatellite instability (MSI) status (microsatellite stable

(MSS), microsatellite instability-high (MSI-H), indeterminate); PD-L1 CPS1 (CPS ≥1, CPS<1, indeterminate); PD-L1 CPS10 (CPS≥10, CPS<10, indeterminate); ECOG performance status at randomization (0 vs. 1).

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above. If the number of participants in a category of a subgroup variable was less than 5% of the ITT population, the subgroup analysis could not be performed for that category of the subgroup variable. The subgroup analyses for PFS and OS were conducted using an unstratified Cox model, and the subgroup analyses for ORR were conducted using the unstratified Miettinen and Nurminen method.

Safety analyses

Safety analyses were based on the All Participants as Treated (APaT) population, which included all 1063 randomized participants who received at least 1 dose of study intervention; participants were analyzed according to the study intervention they received. The primary safety analyses will include only events that occurred before the Second Course Treatment. The analysis of safety results followed a tiered approach. There were no Tier 1 endpoints in this study, and Tier 2 parameters were 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, an unconditional, asymptotic method. Membership in Tier 2 required that at least 10% of participants in any treatment group exhibit the event. All other adverse experiences belonged to Tier 3; only point estimates by intervention arm were provided for Tier 3 safety parameters. Because many 95% CIs were provided without adjustment for multiplicity, the analysis represents a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences.

ePRO analysis

The patient-reported outcomes (PRO) were tertiary/exploratory objectives in KEYNOTE-966, and thus no formal hypotheses were formulated. Nominal p-value to compare the pembrolizumab plus gemcitabine/cisplatin arm to placebo plus gemcitabine/cisplatin arm might be provided as appropriate. The PRO instruments are EORTC QLQ-C30, EORTC QLQ-BIL21 and EQ-5D-5L. The PRO analyses were based on the PRO full analysis set (FAS) population, defined as participants who had received at least 1 dose of study intervention and had completed at least 1 PRO assessment. Participants were analyzed in the intervention group to which they were randomized. PRO FAS populations might be different across EORTC QLQ-C30, EORTC QLQ-BIL21, and EQ-5D-5L.

Results

Participant flow

Figure 5 KEYNOTE-966: Participant flow

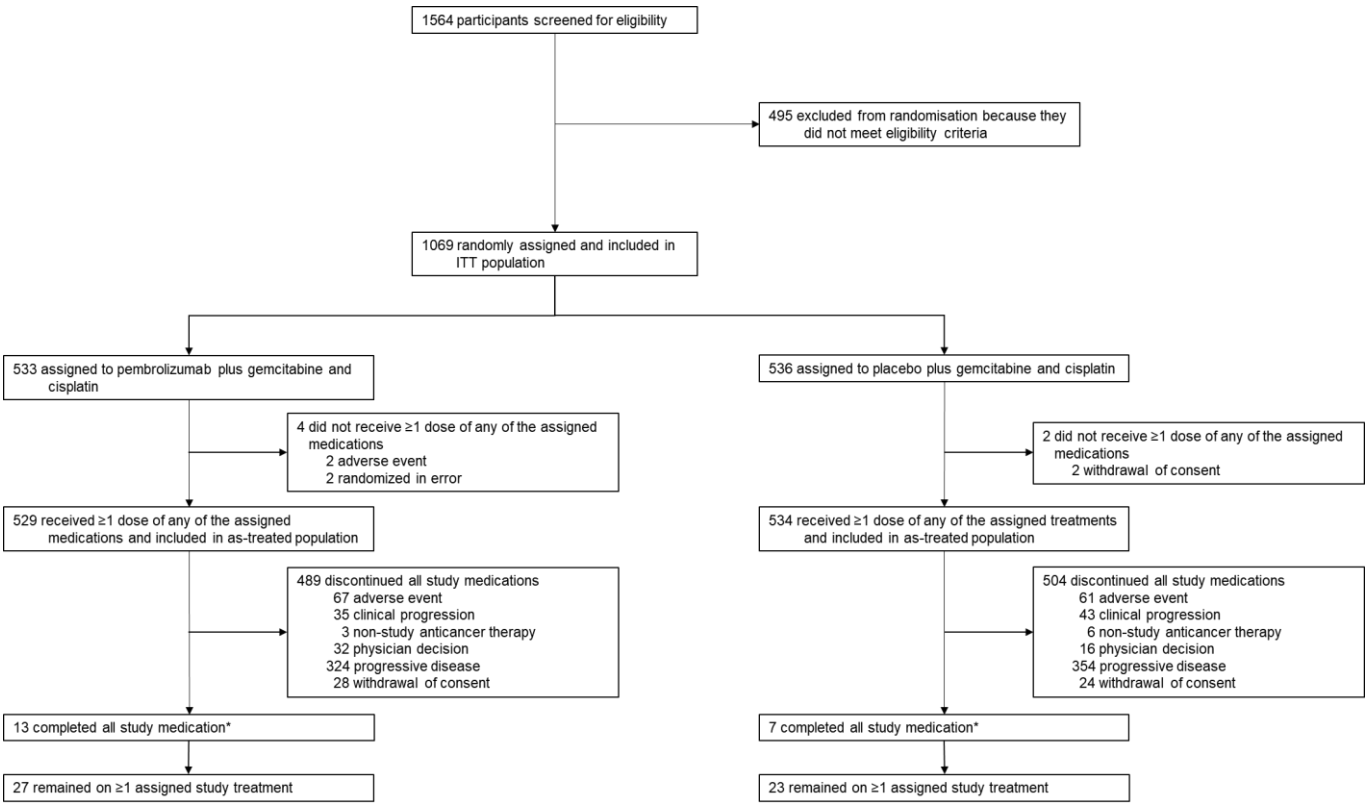


Table 13 Disposition of participants (ITT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	533		536		1069	
Status for Trial						
Started	533		536		1069	
Discontinued	414	(77.7)	446	(83.2)	860	(80.4)
Death	409	(76.7)	443	(82.6)	852	(79.7)
Associated with COVID-19	1	(0.2)	6	(1.1)	7	(0.7)
Unassociated with COVID-19	394	(73.9)	426	(79.5)	820	(76.7)
Unknown association with COVID-19	14	(2.6)	11	(2.1)	25	(2.3)
Lost To Follow-Up	0	(0.0)	1	(0.2)	1	(0.1)
Unknown association with COVID-19	0	(0.0)	1	(0.2)	1	(0.1)
Withdrawal By Subject	5	(0.9)	2	(0.4)	7	(0.7)
Unassociated with COVID-19	0	(0.0)	2	(0.4)	2	(0.2)
Unassociated with COVID-19, Subsequently died	5	(0.9)	0	(0.0)	5	(0.5)
Participants Ongoing	119	(22.3)	90	(16.8)	209	(19.6)
Status for Study Medication in Trial Segment Treatment						
Started	529		534		1063	
Completed[a]	13	(2.5)	7	(1.3)	20	(1.9)
Discontinued	489	(92.4)	504	(94.4)	993	(93.4)
Adverse Event	67	(12.7)	61	(11.4)	128	(12.0)
Associated with COVID-19	0	(0.0)	3	(0.6)	3	(0.3)
Unassociated with COVID-19	67	(12.7)	57	(10.7)	124	(11.7)
Unknown association with COVID-19	0	(0.0)	1	(0.2)	1	(0.1)
Clinical Progression	35	(6.6)	43	(8.1)	78	(7.3)
Unassociated with COVID-19	35	(6.6)	43	(8.1)	78	(7.3)
Non-Study Anti-Cancer Therapy	3	(0.6)	6	(1.1)	9	(0.8)
Unassociated with COVID-19	3	(0.6)	6	(1.1)	9	(0.8)
Physician Decision	32	(6.0)	16	(3.0)	48	(4.5)
Unassociated with COVID-19	32	(6.0)	16	(3.0)	48	(4.5)
Progressive Disease	324	(61.2)	354	(66.3)	678	(63.8)
Unassociated with COVID-19	322	(60.9)	351	(65.7)	673	(63.3)
Unknown association with COVID-19	2	(0.4)	2	(0.4)	4	(0.4)
Unreported association with COVID-19	0	(0.0)	1	(0.2)	1	(0.1)
Withdrawal By Subject	28	(5.3)	24	(4.5)	52	(4.9)
Unassociated with COVID-19	27	(5.1)	24	(4.5)	51	(4.8)
Unknown association with COVID-19	1	(0.2)	0	(0.0)	1	(0.1)
Participants Ongoing	27	(5.1)	23	(4.3)	50	(4.7)
Status for Study Medication in Trial Segment Second Course Treatment						
Started	2		0		2	
Discontinued	2	(100.0)	0	(0.0)	2	(100.0)
Progressive Disease	2	(100.0)	0	(0.0)	2	(100.0)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.

Each participant is counted once for Trial Status based on the latest Survival Follow-up record.

Each participant is counted once for Study Medication Status based on the latest corresponding disposition record.

[a] Completed: participants completed 35 cycles pembrolizumab/placebo at the time of all treatment discontinuation without alternative reasons for discontinuation of any drug if given beyond 35 cycles of pembrolizumab/placebo in the first course treatment

Database Cutoff Date: 15DEC2022

Median duration of follow-up for the FA in the ITT population, defined as the time from randomization to death or DCO, whichever was earlier, was 12.7 months (range: 0.2, 37.5 months) and 10.9 months (range: 0.2, 36.2 months) in the pembrolizumab plus chemotherapy group and placebo plus chemotherapy group, respectively.

The median time from randomization to DCO in the ITT population was 25.6 months (range 18.3 to 38.4 months) for the FA. Certain efficacy analyses presented are based on the IA1 DCO (15-DEC-2021) and the median time from randomization to DCO in the ITT population for IA1 was 13.6 months (range 6.3 to 26.4 months).

Recruitment

The study was conducted in 185 centres in 24 countries/regions. Clinical investigator study sites were located in the following countries/regions: Argentina, Australia, Belgium, Brazil, Canada, Chile, China, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Malaysia, Netherlands, New Zealand, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, and the US.

A total of 1564 participants were screened, and 495 nonrandomized participants were screen failures. Nonrandomized participants who did not meet inclusion criteria or meet exclusion criteria are summarized below:

Table 14 Summary of non-randomized participants who did not meet inclusion criteria or did meet exclusion criteria

		n	(%)
	Non-randomized participants	495	
	Non-randomized participants who did not meet inclusion criteria or did meet exclusion criteria	495	
Code	**Inclusion Criteria**		
IN12_01	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. Refer Protocol for Table 3.	99	(20.0)
IN09_01	Have a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior to the first dose of study intervention.	49	(9.9)
IN12_00	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. Refer Protocol for Table 3.	42	(8.5)
IN10_01	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, paraffinembedded (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.	41	(8.3)
IN08_01	The participant (or legally acceptable representative, if applicable) provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may enroll in the main study without participating in future biomedical research.	40	(8.1)
IN12_02	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. Refer Protocol for Table 3.	25	(5.1)
IN01_01	Has histologically confirmed diagnosis of advanced (metastatic) and/or unresectable (locally advanced) biliary tract cancer (intra-or extrahepatic cholangiocarcinoma or gallbladder cancer).	21	(4.2)
IN08_00	The participant (or legally acceptable representative, if applicable) provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may enroll in the main study without participating in future biomedical research.	19	(3.8)
IN10_00	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 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.	18	(3.6)
IN04_01	Participants with controlled hepatitis B are eligible for the study, as long as they meet the following criteria: Please refer protocol for further details.	13	(2.6)
IN09_00	Have a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior to the first dose of study intervention.	13	(2.6)
IN11_01	Have a life expectancy of greater than 3 months.	13	(2.6)
IN02_01	Have 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 demonstrated in such lesions and they meet criteria for measurable disease per RECIST 1.1.	10	(2.0)
IN02_00	Have 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 demonstrated in such lesions and they meet criteria for measurable disease.	7	(1.4)

As of the DCO (15-DEC-2022) for the FA, a total of 1069 participants were randomized in the ITT population (533 in the pembrolizumab plus chemotherapy group and 536 in the placebo plus chemotherapy group).

Conduct of the study

Changes in the conduct of the study implemented by protocol amendment are summarized in the following table. There were no changes in the planned conduct of the study implemented by protocol amendment due to the COVID-19 pandemic.

Table 15 KEYNOTE-966: Summary of changes in the conduct of the study implemented by protocol amendment

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 to address health agency feedback by clarifying PFS and ORR analyses approach.
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 as requested by the FDA. In addition, China-specific updates were made to address a CDE request. 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.
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 feedback from regulatory authorities, add additional blood sample required for retrospective MSI testing and minimize unnecessary participant visits and procedures.
Original Protocol	21-JUN-2019	Not applicable.

CDE=Center for Drug Evaluation; FDA=Food and Drug Administration; irAE=immune-related adverse event; MSI=microsatellite instability; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; USPI=United States Package Insert.

Important protocol deviations were reported for 95 participants (8.9%). Of these, 30 (2.8%) participants had important protocol deviations that were considered to be clinically important (Table 16). Most of the protocol deviations considered to be clinically important (n=15, 1.4%) were due to improperly stored study intervention.

A listing of important protocol deviations is presented by participant, study site, and clinical importance in the table below. No participant's data were excluded from analyses due to an important protocol deviation. One deviation was classified as a serious GCP compliance issue. This involved the use of incorrect ALT reference ranges caused by a change in equipment in which 1 participant was enrolled but later identified to not meet eligibility ALT criteria based on the correct reference ranges. It was determined that there was no impact to safety.

Table 16 Summary of important protocol deviations considered to be clinically important (ITT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	533		536		1,069	
with one or more clinically important protocol deviations	13	(2.4)	17	(3.2)	30	(2.8)
with no clinically important protocol deviations	520	(97.6)	519	(96.8)	1,039	(97.2)
Discontinuation Criteria	**2**	**(0.4)**	**5**	**(0.9)**	**7**	**(0.7)**
Participant developed study intervention discontinuation criteria, but was not discontinued from study intervention.	2	(0.4)	5	(0.9)	7	(0.7)
Inclusion/ Exclusion Criteria	**0**	**(0.0)**	**4**	**(0.7)**	**4**	**(0.4)**
Participant was not receiving anti-viral therapy for Hepatitis B as required per protocol at randomization.	0	(0.0)	2	(0.4)	2	(0.2)
Participant who did not demonstrate adequate organ function during the screening period prior to the start of study treatment. Total bilirubin <= 1.5*ULN, Direct bilirubin <= ULN for participants with total bilirubin levels > 1.5*ULN, INR or PT/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.	0	(0.0)	2	(0.4)	2	(0.2)
Study Intervention	**11**	**(2.1)**	**6**	**(1.1)**	**17**	**(1.6)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	9	(1.7)	6	(1.1)	15	(1.4)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	2	(0.4)	0	(0.0)	2	(0.2)
Trial Procedures	**0**	**(0.0)**	**2**	**(0.4)**	**2**	**(0.2)**
Pembrolizumab dose modification guidance not followed for SAEs and HECIs (eg, not holding dose for toxicities as indicated in the protocol), including when a participant develops an adverse event for which the protocol instructs study treatment discontinuation, but treatment was not discontinued.	0	(0.0)	2	(0.4)	2	(0.2)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 15DEC2022.						

Part of this study was conducted during the COVID-19 pandemic.

Table 17 Measures implemented by the sponsor to manage study conduct during the COVID-19 pandemic for KEYNOTE-966

Process	Measure (Date Implemented/Date Ended: DD-MMM-YYYY)
Study site monitoring	• Modifications to the frequency of onsite and remote monitoring were allowed due to national and local travel restrictions and/or study site restrictions to onsite monitoring (21-MAR-2020). • Redacted/alternate methods for source data review and verification for critical data points in absence of remote access to electronic medical records were allowed under documented circumstances (06-MAR-2020). • Source data review and/or verification before database lock was/were waived for this study (13-MAR-2020). • Critical data points for SDV were reassessed and the SMP updated without the usual approval workflow approval for resumption of onsite monitoring (01-MAY-2020).
Protocol deviations	• Study sites were queried as to the relationship of reported deviations to the COVID-19 pandemic; responses were documented (20-MAR-2020).
AE reporting	• COVID-19 infection was to be reported following the protocol's AE and SAE reporting instructions.
Clinical supplies (including study intervention)	• Direct shipping of ambient drug, without temperature monitoring, from the study site to study participants was allowed under specific circumstances (eg, stability data support transit time) (30-MAR-2020). • An alternate location (eg, primary care center, pharmacy) for injectable and/or infusion administration of study intervention/other clinical supplies was allowed when participant travel was impacted, and administration could not be postponed (21-APR-2020).
Data management	• Alternative procedures were allowed for study sites using shared electronic devices to complete clinical outcome assessments (08-APR-2020). • Study sites were queried, and responses documented about the relationship of the following to the COVID-19 pandemic (08-APR-2020): - Missing participant study visits and data. - Participants who discontinued study intervention and/or the study.
Informed consent	• Oral confirmation of participant consent (eg, via telephone) was allowed when in-person discussion and signature was not possible (30-MAR-2020).

Baseline data

Table 18 Participant characteristics (ITT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	533		536		1,069	
Sex						
Male	280	(52.5)	272	(50.7)	552	(51.6)
Female	253	(47.5)	264	(49.3)	517	(48.4)
Age (Years)						
< 65	269	(50.5)	298	(55.6)	567	(53.0)
>= 65	264	(49.5)	238	(44.4)	502	(47.0)
Mean	63.3		61.8		62.5	
SD	10.3		11.0		10.7	
Median	64.0		63.0		64.0	
Range	23 to 85		28 to 84		23 to 85	
Race						
American Indian Or Alaska Native	2	(0.4)	1	(0.2)	3	(0.3)
Asian	245	(46.0)	250	(46.6)	495	(46.3)
Black Or African American	11	(2.1)	3	(0.6)	14	(1.3)
Multiple	5	(0.9)	2	(0.4)	7	(0.7)
American Indian Or Alaska Native, Black Or African American	1	(0.2)	0	(0.0)	1	(0.1)
American Indian Or Alaska Native, Black Or African American, White	0	(0.0)	1	(0.2)	1	(0.1)
Black Or African American, White	2	(0.4)	1	(0.2)	3	(0.3)
White, Asian	2	(0.4)	0	(0.0)	2	(0.2)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	0	(0.0)	1	(0.1)
White	256	(48.0)	268	(50.0)	524	(49.0)
Missing	13	(2.4)	12	(2.2)	25	(2.3)
Ethnicity						
Hispanic Or Latino	59	(11.1)	52	(9.7)	111	(10.4)
Not Hispanic Or Latino	433	(81.2)	449	(83.8)	882	(82.5)
Not Reported	32	(6.0)	31	(5.8)	63	(5.9)
Unknown	5	(0.9)	3	(0.6)	8	(0.7)
Missing	4	(0.8)	1	(0.2)	5	(0.5)
Geographic Region (by Stratification Factor)						

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Asia	242	(45.4)	244	(45.5)	486	(45.5)
Non-Asia	291	(54.6)	292	(54.5)	583	(54.5)
Geographic Region						
North America	45	(8.4)	40	(7.5)	85	(8.0)
Western Europe	151	(28.3)	151	(28.2)	302	(28.3)
Rest of the World	337	(63.2)	345	(64.4)	682	(63.8)
Prior Adjuvant Therapy						
Yes	47	(8.8)	48	(9.0)	95	(8.9)
No	486	(91.2)	488	(91.0)	974	(91.1)
Prior Neo-adjuvant Therapy						
Yes	3	(0.6)	1	(0.2)	4	(0.4)
No	530	(99.4)	535	(99.8)	1,065	(99.6)
Prior Surgery						
Yes	157	(29.5)	162	(30.2)	319	(29.8)
No	376	(70.5)	374	(69.8)	750	(70.2)
Prior Radiation						
Yes	21	(3.9)	28	(5.2)	49	(4.6)
No	512	(96.1)	508	(94.8)	1,020	(95.4)
Prior Chemotherapy						
Yes	50	(9.4)	48	(9.0)	98	(9.2)
No	483	(90.6)	488	(91.0)	971	(90.8)
Prior PDT						
No	533	(100.0)	536	(100.0)	1,069	(100.0)
PD-L1 Status (CPS>=1)						
CPS<1	113	(21.2)	110	(20.5)	223	(20.9)
CPS>=1	363	(68.1)	365	(68.1)	728	(68.1)
Indeterminate	57	(10.7)	61	(11.4)	118	(11.0)
PD-L1 Status (CPS>=10)						
CPS<10	273	(51.2)	289	(53.9)	562	(52.6)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
CPS>=10	203	(38.1)	186	(34.7)	389	(36.4)
Indeterminate	57	(10.7)	61	(11.4)	118	(11.0)
MSI Status						
MSI-H	6	(1.1)	4	(0.7)	10	(0.9)
MSS	433	(81.2)	422	(78.7)	855	(80.0)
Indeterminate	94	(17.6)	110	(20.5)	204	(19.1)
ECOG Performance Status						
0	258	(48.4)	228	(42.5)	486	(45.5)
1	274	(51.4)	308	(57.5)	582	(54.4)
>=2	1	(0.2)	0	(0.0)	1	(0.1)
Site of Origin						
Gallbladder	115	(21.6)	118	(22.0)	233	(21.8)
Intrahepatic	320	(60.0)	313	(58.4)	633	(59.2)
Extrahepatic	98	(18.4)	105	(19.6)	203	(19.0)
Disease Status						
Locally Advanced	60	(11.3)	66	(12.3)	126	(11.8)
Metastatic	473	(88.7)	470	(87.7)	943	(88.2)
Hepatitis B Status						
Chronic HBV Infection	14	(2.6)	16	(3.0)	30	(2.8)
Clinically Resolved HBV Infection	150	(28.1)	149	(27.8)	299	(28.0)
Negative	366	(68.7)	366	(68.3)	732	(68.5)
Missing	3	(0.6)	5	(0.9)	8	(0.7)
Any Viral Hepatitis B						
HBV Infection	164	(30.8)	165	(30.8)	329	(30.8)
Negative	366	(68.7)	366	(68.3)	732	(68.5)
Missing	3	(0.6)	5	(0.9)	8	(0.7)
Hepatitis C Status						
HCV Infection	1	(0.2)	1	(0.2)	2	(0.2)
Prior HCV Infection	18	(3.4)	13	(2.4)	31	(2.9)
Negative	514	(96.4)	520	(97.0)	1,034	(96.7)
Missing	0	(0.0)	2	(0.4)	2	(0.2)
Any Viral Hepatitis C						
HCV Infection	19	(3.6)	14	(2.6)	33	(3.1)
Negative	514	(96.4)	520	(97.0)	1,034	(96.7)
Missing	0	(0.0)	2	(0.4)	2	(0.2)
Smoking Status						
Never Smoker	272	(51.0)	295	(55.0)	567	(53.0)
Former Smoker	205	(38.5)	191	(35.6)	396	(37.0)
Current Smoker	56	(10.5)	49	(9.1)	105	(9.8)
Missing	0	(0.0)	1	(0.2)	1	(0.1)
Alcohol Use Status						
Never Used Alcohol	282	(52.9)	316	(59.0)	598	(55.9)
Used/Using Alcohol	251	(47.1)	219	(40.9)	470	(44.0)
Missing	0	(0.0)	1	(0.2)	1	(0.1)
Disease Overall Stage						
I	3	(0.6)	2	(0.4)	5	(0.5)
II	19	(3.6)	15	(2.8)	34	(3.2)
III	36	(6.8)	47	(8.8)	83	(7.8)
IV	475	(89.1)	472	(88.1)	947	(88.6)
Biliary Stent/Biliary Drain						
Yes	33	(6.2)	41	(7.6)	74	(6.9)
No	500	(93.8)	495	(92.4)	995	(93.1)
Antibiotics within 1 month of study start						
Yes	62	(11.6)	43	(8.0)	105	(9.8)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
No	471	(88.4)	493	(92.0)	964	(90.2)

Asia: Korea, Republic of, Taiwan, Hong Kong, Thailand, Japan, China and Malaysia

Non-Asia: Argentina, Australia, Belgium, Brazil, Canada, Chile, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Spain, Turkey, United Kingdom and United States

North America: Canada and United States

Western Europe: Belgium, France, Germany, Ireland, Italy, Netherlands, Spain and United Kingdom

Rest of the World: Argentina, Australia, Brazil, Chile, China, Hong Kong, Israel, Japan, Korea, Republic of, Malaysia, New Zealand, Taiwan, Thailand and Turkey

Chronic HBV Infection: participants hepatitis B virus surface antigen positive, and/or hepatitis B DNA is numeric value (excluding "<20 IU/mL").

Clinically Resolved HBV Infection: participants hepatitis B virus surface antigen negative, and hepatitis B DNA is not detectable or "<20 IU/mL" and (hepatitis B Core IgG and IgM antibodies positive or hepatitis B virus core IgM antibody positive).

Hepatitis B Status Negative: participants hepatitis B virus surface antigen negative, and hepatitis B DNA is not detectable or "<20 IU/mL" and (hepatitis B Core IgG and IgM antibodies negative or hepatitis B virus core IgM antibody negative).

Chronic HCV Infection: participants with hepatitis C IgG antibody positive and hepatitis C virus RNA is numeric value

Prior HCV Infection: participants with hepatitis C IgG antibody positive and hepatitis C virus RNA is not detectable.

Hepatitis C Status Negative: participants with hepatitis C IgG antibody negative.

HBV Infection: participants with either chronic HBV infection or clinically resolved HBV infection.

HCV Infection: participants with either chronic HCV infection or prior HCV infection.

Database Cutoff Date: 15DEC2022.

Table 19 Metastatic sites of disease at Baseline (ITT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	533		536	
Metastatic sites of disease — no. (%)	**473**	**(88.7)**	**470**	**(87.7)**
Liver	314	(58.9)	300	(56.0)
Lymph node	310	(58.2)	293	(54.7)
Respiratory	159	(29.8)	146	(27.2)
Peritoneum	130	(24.4)	130	(24.3)
Musculoskeletal and soft tissue	63	(11.8)	68	(12.7)
Abdomen wall, cavity and organs (other than liver)	42	(7.9)	57	(10.6)
Biliary tract and gall bladder	31	(5.8)	30	(5.6)
Ascites	14	(2.6)	12	(2.2)
Others	12	(2.3)	16	(3.0)
Database Cutoff Date: 15DEC2022.				

Table 20 Previous modalities of anticancer treatment (ITT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	533		536	
Chemotherapy	**50**	**(9.4)**	**48**	**(9.0)**
Radiotherapy	**21**	**(3.9)**	**28**	**(5.2)**
Previous surgical therapy related to disease under study (except biliary stenting or drainage)	**140**	**(26.3)**	**145**	**(27.1)**
Hepatectomy	71	(13.3)	70	(13.1)
Cholecystectomy	45	(8.4)	52	(9.7)
Pancreaticoduodenectomy	32	(6.0)	36	(6.7)
Biliary tract operation	13	(2.4)	16	(3.0)

Tumour excision	4	(0.8)	1	(0.2)
Cancer surgery	4	(0.8)	4	(0.7)
Hepaticojejunostomy	3	(0.6)	6	(1.1)
Cholangiojejunostomy	1	(0.2)	0	(0.0)
Choledochoenterostomy	1	(0.2)	0	(0.0)
Choledocholithotomy	1	(0.2)	0	(0.0)
Pancreatectomy	1	(0.2)	0	(0.0)
Tumour invasion	1	(0.2)	0	(0.0)
Gallbladder operation	1	(0.2)	1	(0.2)
Cholangiocarcinoma	0	(0.0)	1	(0.2)
Liver operation	0	(0.0)	1	(0.2)
Extent of resection				
NEGATIVE (R0)	95	(17.8)	101	(18.8)
POSITIVE (R1)	26	(4.9)	27	(5.0)
POSITIVE (R2)	7	(1.3)	8	(1.5)
Missing	16	(3.0)	14	(2.6)
Locoregional Therapy	**17**	**(3.2)**	**14**	**(2.6)**
Transcatheter arterial chemoembolisation	7	(1.3)	4	(0.7)
High frequency ablation	5	(0.9)	0	(0.0)

Table 21 Previous modalities of anticancer treatment (ITT population) (continued)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Therapeutic embolisation	4	(0.8)	1	(0.2)
Radioembolisation	2	(0.4)	5	(0.9)
Alcoholisation procedure	1	(0.2)	0	(0.0)
Liver ablation	1	(0.2)	1	(0.2)
Microwave therapy	1	(0.2)	1	(0.2)
Tumour ablation	1	(0.2)	1	(0.2)
Regional chemotherapy	1	(0.2)	2	(0.4)
Cryotherapy	0	(0.0)	1	(0.2)
Previous history of biliary stenting or drainage (previous or ongoing)	**33**	**(6.2)**	**41**	**(7.6)**
Bile duct stent insertion	16	(3.0)	17	(3.2)
Biliary catheter insertion	9	(1.7)	18	(3.4)
Cholangiostomy	5	(0.9)	6	(1.1)
Catheter site discharge	1	(0.2)	0	(0.0)
Choledochotomy	1	(0.2)	0	(0.0)
Device occlusion	1	(0.2)	0	(0.0)
Biliary catheter removal	1	(0.2)	2	(0.4)
Drain placement	1	(0.2)	2	(0.4)
Drain removal	1	(0.2)	2	(0.4)
Stent placement	1	(0.2)	6	(1.1)
Stent removal	0	(0.0)	1	(0.2)
Bile duct stent removal	0	(0.0)	2	(0.4)
Database Cutoff Date: 15DEC2022.				

Numbers analysed

Table 22 Study populations

	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy	Total
Number of Participants Screened			1564
Number of Participants Randomized (Planned Treatment) (ITT)	533	536	1069
Number of Participants Received Treatment (Actual Treatment) (APaT)	529	534	1063
Number of Participants Randomized and Did Not Receive Treatment	4	2	6
Database Cutoff Date: 15DEC2022.			

The efficacy analyses were based on the ITT population of 1069 randomized participants except for the DOR analysis that was based on the population of the responders.

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. Participants were analyzed in the intervention group to which they were randomized. PRO FAS populations may be different across EORTC QLQ-C30, EORTC QLQ-BIL21, and EQ-5D-5L.

Outcomes and estimation

Primary efficacy endpoint of OS was analysed at FA. At DCO for FA, 15-DEC-2022 (38.4 months from start of randomization) a total of 857 OS events were observed. The analyses of PFS, ORR, and DOR (secondary endpoints) were prespecified in the protocol to be based on IA1 data (15-DEC-2021 DCO). Descriptive analyses for secondary endpoints of PFS, ORR and DOR based on FA were also provided.

Primary Endpoint

OS

Figure 6 Kaplan-Meier Estimates of Overall Survival (ITT population)

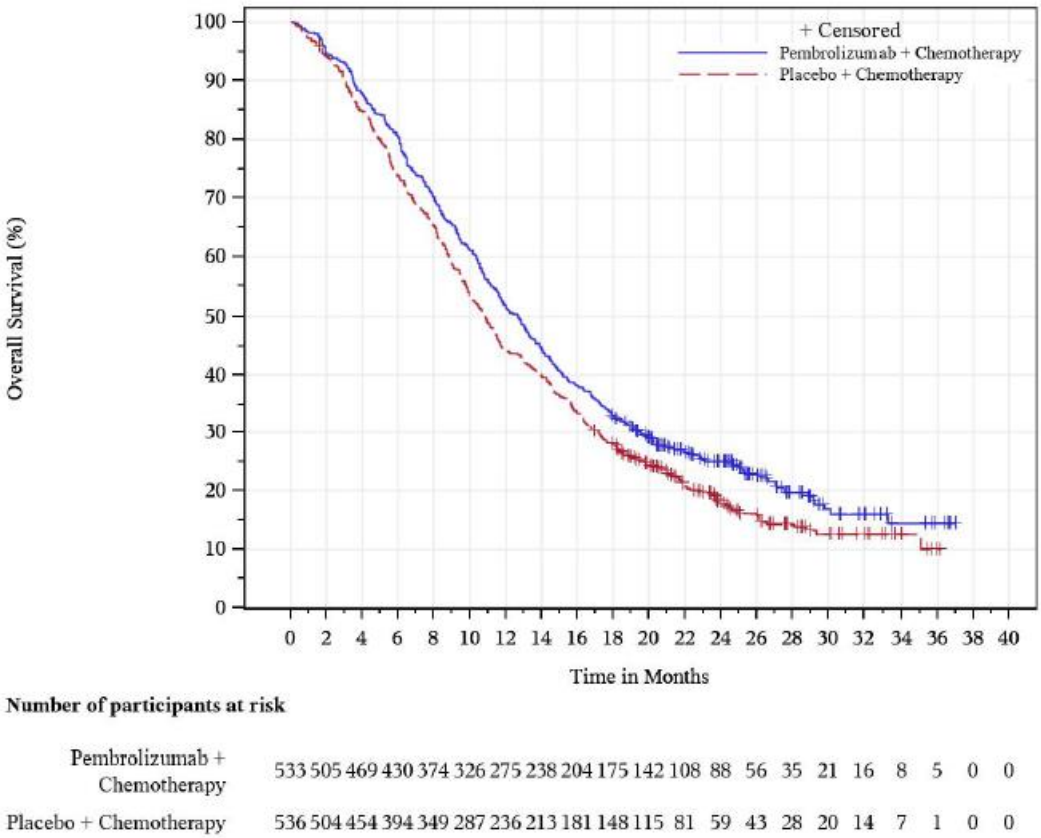


Table 23 Analysis of Overall Survival (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS[a] (months) (95% CI)
Pembrolizumab + Chemotherapy	533	414 (77.7)	7473.3	5.5	12.7 (11.5, 13.6)
Placebo + Chemotherapy	536	443 (82.6)	6799.6	6.5	10.9 (9.9, 11.6)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.83 (0.72, 0.95)		0.0034[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Non-Asia), disease status (locally advanced versus metastatic), site of origin (gallbladder versus intrahepatic versus extrahepatic) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Non-Asia), disease status (locally advanced versus metastatic), site of origin (gallbladder versus intrahepatic versus extrahepatic) with small strata collapsed as pre-specified in the sSAP.
Database Cutoff Date: 15DEC2022.

Table 24 Summary of Overall Survival Rate Over Time (ITT population)

	Pembrolizumab + Chemotherapy (N=533) % (95% CI)[a]	Placebo + Chemotherapy (N=536) % (95% CI)[a]
Summary of Overall Survival rate at time point		
6 months	80.7 (77.1, 83.8)	73.7 (69.7, 77.2)
12 months	51.6 (47.3, 55.7)	44.1 (39.9, 48.3)
18 months	33.0 (29.1, 37.0)	28.0 (24.3, 31.9)
24 months	24.9 (21.2, 28.8)	18.1 (14.8, 21.7)

[a] From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 15DEC2022.

Secondary Endpoint

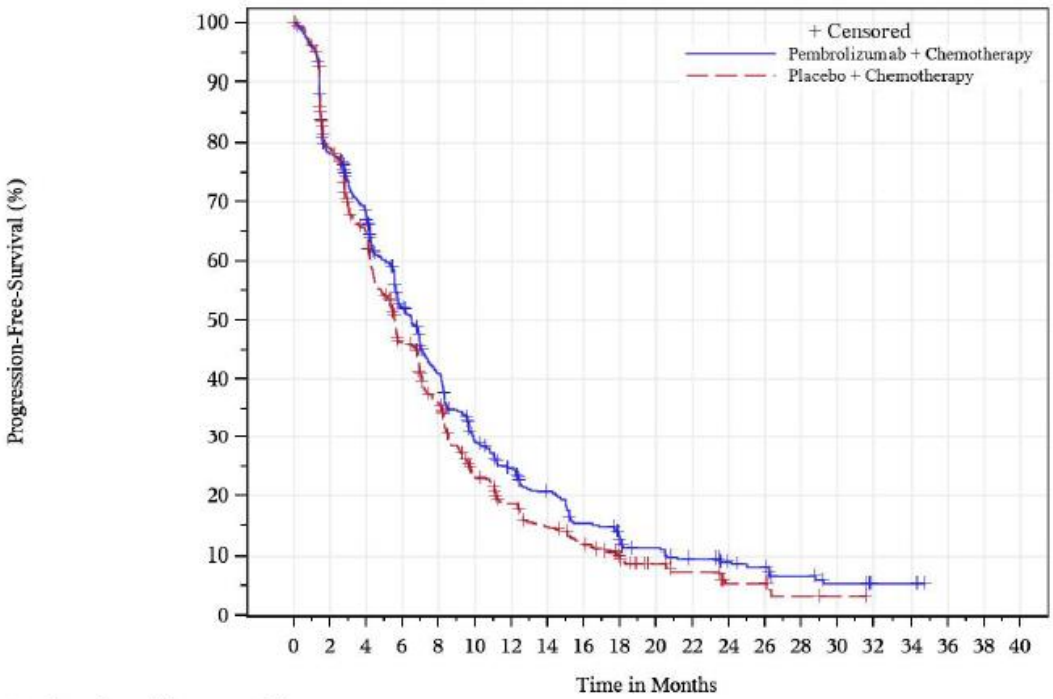
PFS

At IA1 (15-DEC-2021), the observed point estimate for PFS HR favoured pembrolizumab plus chemotherapy though it did not meet statistical significance when compared with placebo plus chemotherapy (HR=0.86; 95% CI: 0.75, 1.00; p=0.0225); the p-value was greater than the p-value boundary of 0.0125 for statistical significance.

Median PFS was 6.5 months (95% CI: 5.7, 6.9) in the pembrolizumab plus chemotherapy and 5.6 months (95% CI: 5.1, 6.6) in the placebo plus chemotherapy groups, respectively.

Results at FA (DCO 15-DEC-2022) are shown below:

Figure 7 Kaplan-Meier Estimates of Progression-free Survival at FA (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT population)



Database Cutoff Date: 15DEC2022.

Table 25 Analysis of Progression-free Survival at FA (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	533	428 (80.3)	3931.9	10.9	6.5 (5.7, 6.9)
Placebo + Chemotherapy	536	448 (83.6)	3532.2	12.7	5.6 (4.9, 6.5)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.87 (0.76, 0.99)		0.0171[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Non-Asia), disease status (locally advanced versus metastatic), site of origin (gallbladder versus intrahepatic versus extrahepatic) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Non-Asia), disease status (locally advanced versus metastatic), site of origin (gallbladder versus intrahepatic versus extrahepatic) with small strata collapsed as pre-specified in the sSAP.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

ORR

At IA1(15-DEC-2021), ORR based on BICR assessment by RECIST 1.1 was 28.7% (95% CI: 24.9, 32.8) for pembrolizumab plus chemotherapy and 28.5% (95% CI: 24.8, 32.6) for placebo plus chemotherapy

and did not meet the prespecified criterion for statistical significance (between-group difference=0.2 [95% CI: −5.2, 5.6]; p=0.4735).

Results at FA (DCO 15-DEC-2022) are shown below:

Table 26 Summary of Best Overall Response with Confirmation at FA Based on BICR Assessment per RECIST 1.1 (ITT population)

Response Evaluation	Pembrolizumab + Chemotherapy			Placebo + Chemotherapy		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	533			536		
Complete Response (CR)	14	2.6	(1.4, 4.4)	9	1.7	(0.8, 3.2)
Partial Response (PR)	142	26.6	(22.9, 30.6)	143	26.7	(23.0, 30.6)
Objective Response Rate (CR+PR)	**156**	**29.3**	**(25.4, 33.3)**	**152**	**28.4**	**(24.6, 32.4)**
Stable Disease (SD)[b]	243	45.6	(41.3, 49.9)	253	47.2	(42.9, 51.5)
Disease Control (CR+PR+SD)	**399**	**74.9**	**(71.0, 78.5)**	**405**	**75.6**	**(71.7, 79.1)**
Progressive Disease (PD)	104	19.5	(16.2, 23.1)	97	18.1	(14.9, 21.6)
Non-evaluable (NE)	8	1.5	(0.7, 2.9)	11	2.1	(1.0, 3.6)
No Assessment	22	4.1	(2.6, 6.2)	23	4.3	(2.7, 6.4)

[a] Based on binomial exact confidence interval method.
[b] Stable disease includes SD, Non-CR/Non-PD and NED.
BICR = Blinded independent central review.
NE: post-baseline assessment(s) available however not being evaluable.
No Assessment: no post-baseline assessment(s) available for response evaluation.
Database Cutoff Date: 15DEC2022.

DoR

At IA1 (15-DEC-2021), among responders median DOR was longer in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group (9.7 months (1.2+ - 22.7+) vs 6.9 months (0.0+ - 19.2+), respectively).

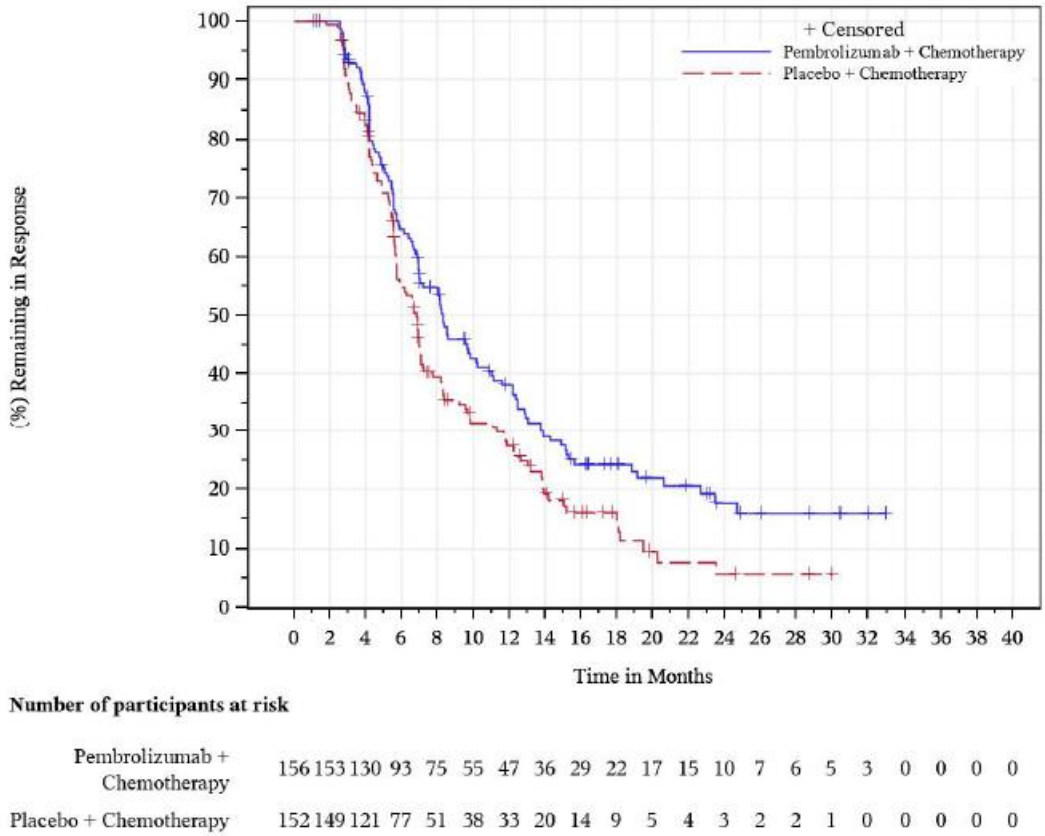
Results at FA (DCO 15-DEC-2022) are shown below:

Table 27 Summary of Time to Response and Duration of Response Based on BICR Assessment per RECIST 1.1 at FA in Participants With Confirmed Response (ITT population)

	Pembrolizumab + Chemotherapy (N=533)	Placebo + Chemotherapy (N=536)
Number of participants with response[a]	156	152
Time to Response (months)		
Mean (SD)	3.4 (3.0)	3.2 (2.0)
Median (Range)	2.8 (1.1-26.2)	2.8 (1.2-12.5)
Response Duration[b] (months)		
Median (Range)	8.3 (1.2+ - 33.0+)	6.8 (1.1+ - 30.0+)
Number (%[b]) of Participants with Extended Response Duration:		
≥3 months	141 (93.5)	134 (90.0)
≥6 months	93 (64.6)	77 (54.7)
≥9 months	61 (45.8)	44 (35.5)
≥12 months	47 (38.0)	33 (27.3)
≥15 months	34 (27.5)	17 (18.1)
≥18 months	22 (24.2)	9 (14.4)
≥21 months	16 (20.5)	4 (7.7)
≥24 months	10 (17.6)	3 (5.7)

[a] Includes participants with confirmed complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022

Figure 8 Kaplan-Meier Estimates of Duration of Response at FA Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response (ITT population)



Database Cutoff Date: 15DEC2022.

Exploratory endpoints

Patient-reported outcomes (PRO)

From baseline to Week 18, the prespecified exploratory PRO endpoints using the EORTC QLQ-C30 (global health status (GHS)/quality of life (QoL), physical functioning, role functioning), EORTC QLQ-BIL21 (pain and jaundice scores), and EQ-5D-5L VAS for participants receiving pembrolizumab plus chemotherapy were similar to those treated with placebo plus chemotherapy. From baseline to Week 18, Health-related Quality of Life (HRQoL) was maintained when pembrolizumab was added to chemotherapy.

For the GHS/QoL and functional domains of the EORTC QLQ-C30, a higher score denotes better health. For the symptom domains of the EORTC QLQ-C30 and EORTC QLQ-BIL21, a higher score indicates worsening of symptoms or more symptom burden.

EORTC QLQ-C30

From baseline to Week 18, LSM changes in the prespecified EORTC QLQ-C30 GHS/QoL, physical functioning, and role functioning scores were similar between the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group.

- The Least squares mean (LSM) score difference for GHS/QoL was 0.04 points (95% CI: -2.52, 2.60), with a nominal p value (not adjusted for multiplicity) of 0.9773.

- The LSM score difference for physical functioning was 1.24 (95% CI: -1.42, 3.90), nominal p-value (not adjusted for multiplicity): 0.3596 and for role functioning was 2.68 (95% CI: -0.76, 6.11), nominal p-value (not adjusted for multiplicity): 0.1264.

- The Time-to-deterioration (TTD) was similar between the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group for GHS/QoL with the median not reached in the pembrolizumab plus chemotherapy group versus 21.22 months in the placebo plus chemotherapy group (HR=0.86, 95% CI: 0.70, 1.07; nominal p=0.1644), physical functioning (median NR vs 11.99 months; HR=0.95, 95% CI: 0.78, 1.17; nominal p=0.6412), and role functioning (median 6.47 months vs 5.75 months; HR=0.98, 95% CI: 0.81, 1.18; nominal p=0.8326).

EORTC QLQ-BIL21

- From baseline to Week 18, LSM changes in EORTC QLQ-BIL21 scores were similar between the 2 treatment groups. LSM score differences were as follows: jaundice=0.26 (95% CI: -1.35, 1.87; nominal p=0.7535), and pain= -1.87 (95% CI: -4.26, 0.53; nominal p=0.1265).

- TTD in EORTC QLQ-BIL21 was similar between the 2 groups for jaundice (median TTD was NR for both groups; HR=1.20; 95% CI: 0.94, 1.54; nominal p=0.1468) and pain (median TTD was NR for both groups; HR=0.79; 95% CI: 0.59, 1.05; nominal p=0.1064).

EQ-5D-5L

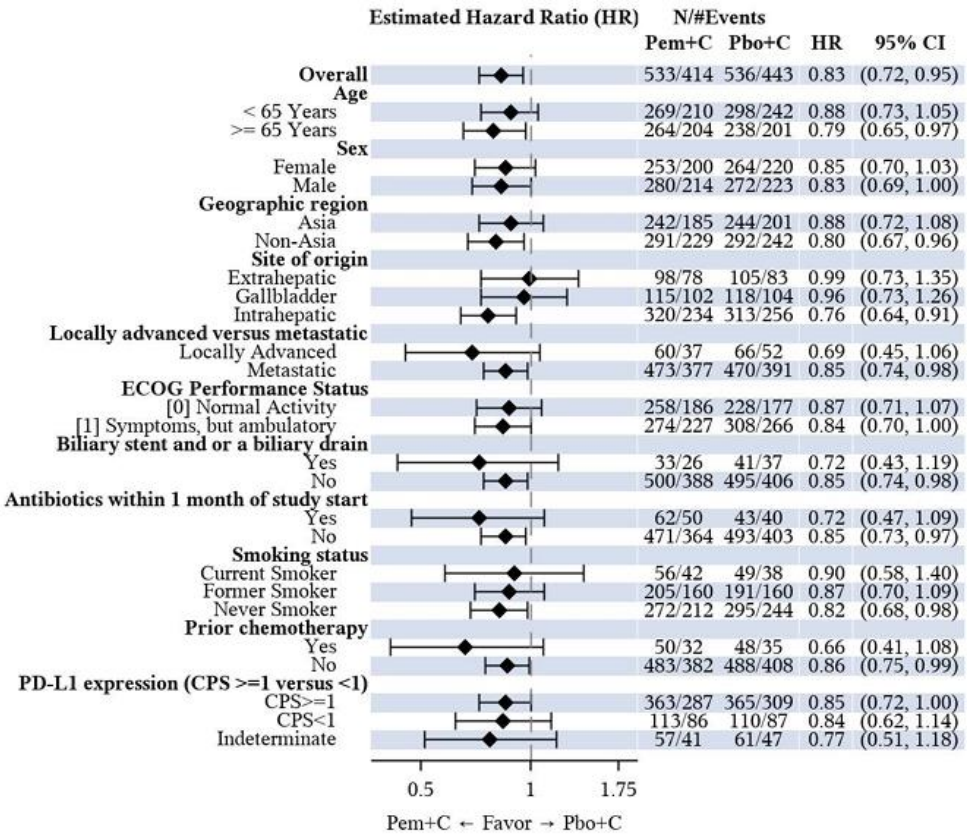
Results from the EQ-5D analyses were consistent with the results of EORTC QLQ-C30 analyses. From baseline to Week 18, LSM changes in EQ-5D-5L VAS scores were similar between the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group. LSM score difference was 0.14 (95% CI: -2.18, 2.46; nominal p=0.9058).

Ancillary analyses

Subgroup analyses

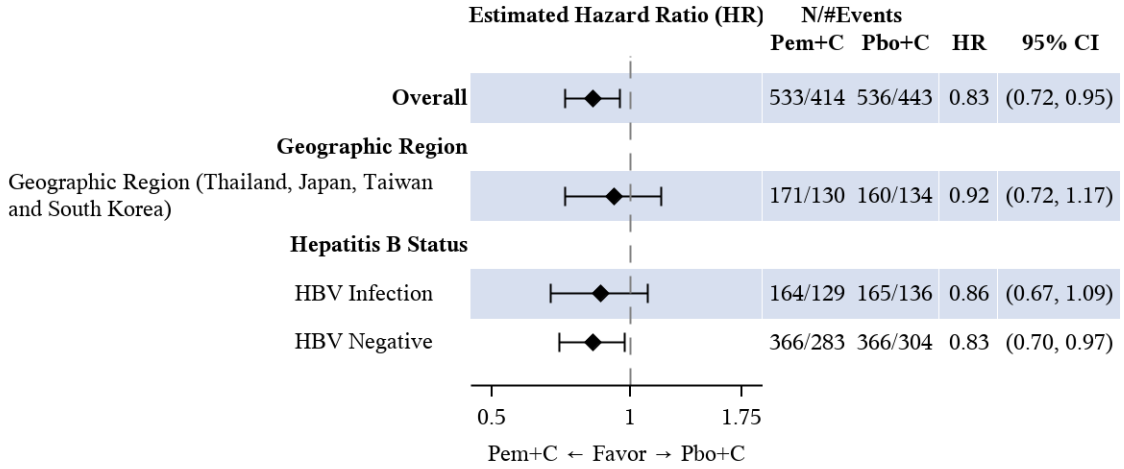
OS

Figure 9 Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (ITT population)



Pem+C = Pembrolizumab + Chemotherapy.
Pbo+C = Placebo + Chemotherapy.
For overall population, analysis is based on the same stratified Cox regression model as conducted for the primary analysis.
Subgroup analyses were conducted using an unstratified Cox model with treatment as a covariate.
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. If there is only one category of a subgroup left (meaning other categories of a subgroup variable are all less than 5% of the ITT population), this subgroup variable will not be displayed in the forest plot.
Database Cutoff Date: 15DEC2022.

Figure 9 (Continued) Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (ITT population)



Pem+C = Pembrolizumab + Chemotherapy.
Pbo+C = Placebo + Chemotherapy.
For overall population, analysis is based on the same stratified Cox regression model as conducted for the primary analysis.
Subgroup analyses were conducted using an unstratified Cox model with treatment as a covariate.
HBV Infection: Participants with either chronic HBV infection or clinically resolved HBV infection.
Database Cutoff Date: 15DEC2022.

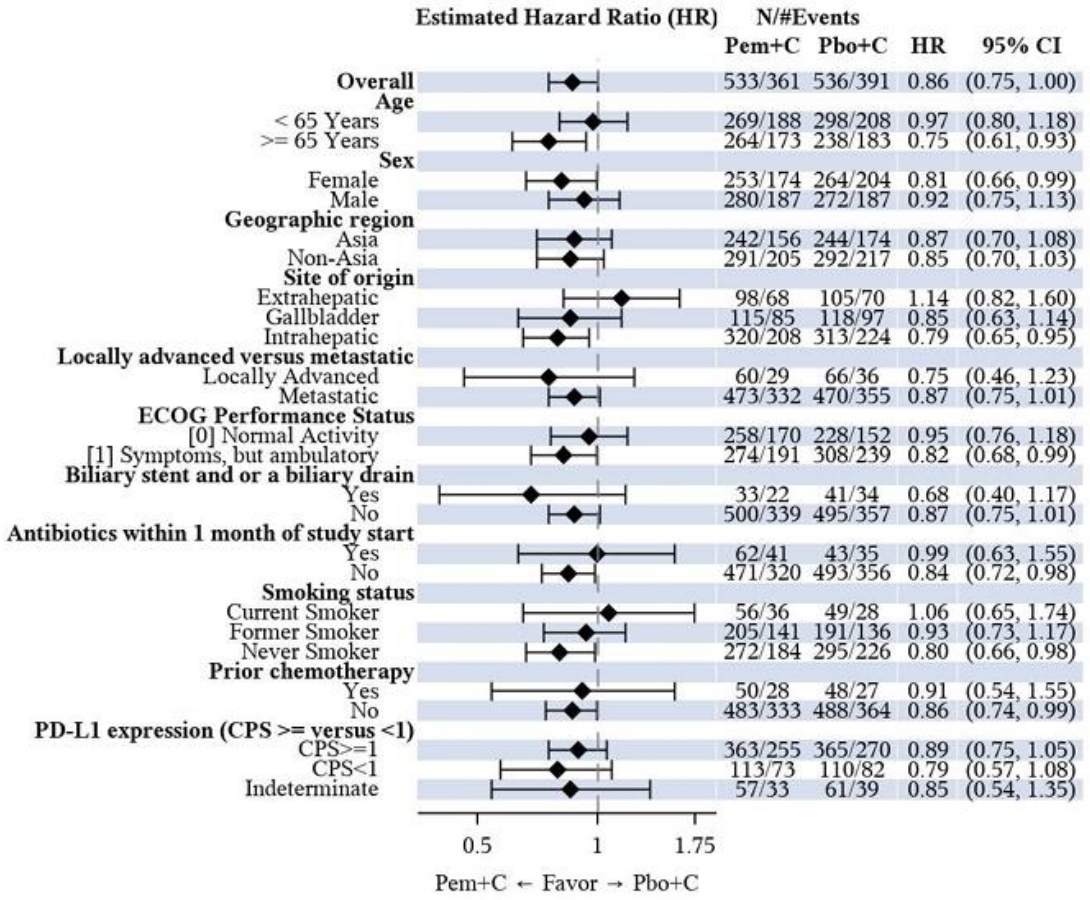
Ad hoc subgroup analysis for OS

An exploratory ad hoc subgroup analysis of a limited geographic region including participants from Thailand, Japan, Taiwan and South Korea (n= 331) was performed and showed a hazard ratio of 0.92 (95% CI: 0.72, 1.17) for OS, favouring the pembrolizumab plus chemotherapy arm.

A subgroup analysis of participants with a history of HBV infection (n= 329) showed a hazard ratio of 0.86 (95% CI: 0.67, 1.09) for OS, favouring the pembrolizumab plus chemotherapy arm. Similarly, participants with no history of HBV infection (n= 732) showed a hazard ratio of 0.83 (95% CI: 0.70, 0.97) for OS, also favouring the pembrolizumab plus chemotherapy arm.

PFS

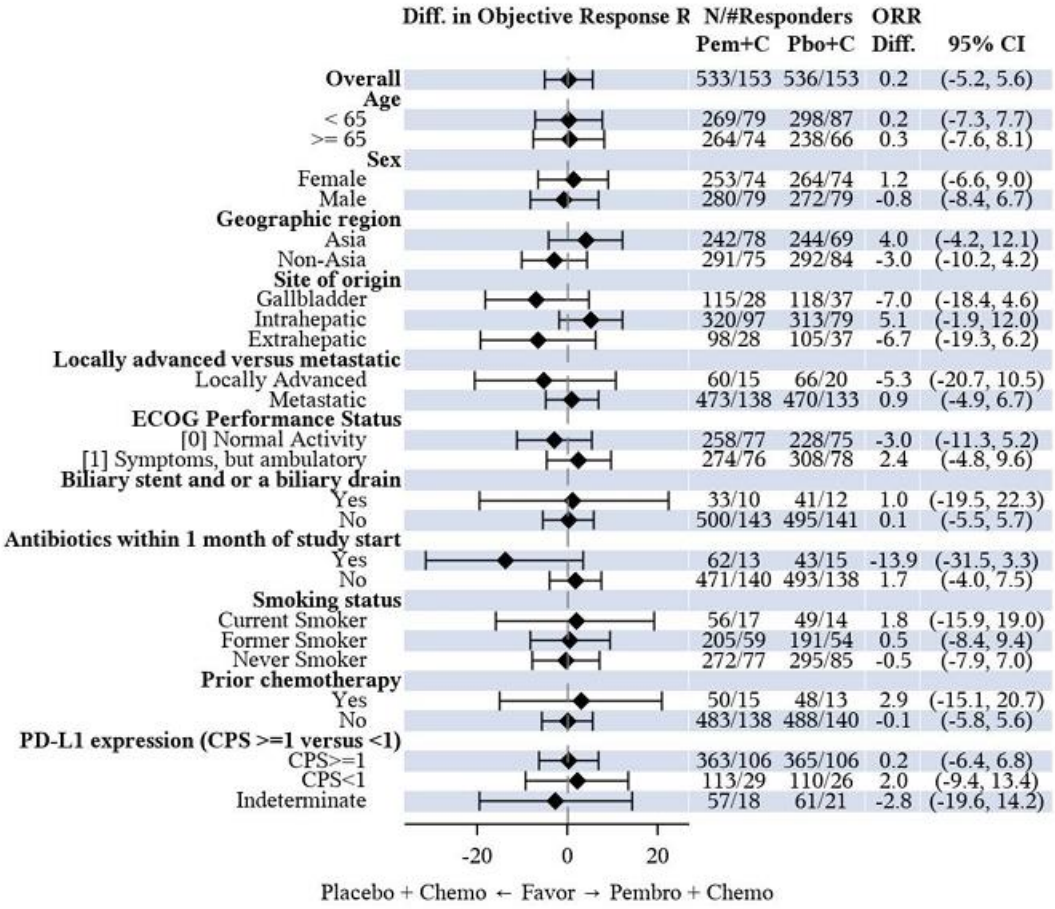
Figure 10 Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors at IA1 Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT population)



Pem+C = Pembrolizumab + Chemotherapy.
Pbo+C = Placebo + Chemotherapy.
For overall population, analysis is based on the same stratified Cox regression model as conducted for the primary analysis.
Subgroup analyses were conducted using an unstratified Cox model with treatment as a covariate.
If the number of participants in a category of a subgroup variable is less than 5% of the ITT population, the subgroup analysis was not performed for this category of the subgroup variable. If there is only one category of a subgroup left (meaning other categories of a subgroup variable are all less than 5% of the ITT population), this subgroup variable was not displayed in the forest plot. Subgroup variables used in the forest plot are from the latest database (i.e., ADSL from FA).
Database Cutoff Date: 15DEC2021.

ORR

Figure 11 Forest Plot of Objective Response Rate with Confirmation by Subgroups Factors at IA1 Based on BICR Assessment per RECIST 1.1 (ITT population)



Pem+C = Pembrolizumab + Chemotherapy.

Pbo+C = Placebo + Chemotherapy.

Analysis (ORR difference and 95% CI) for the overall population is based on the same stratified Miettinen & Nurminen method as conducted for the ORR analysis in ITT population. Subgroup analyses were conducted using the unstratified Miettinen & Nurminen method.

If the number of participants in a category of a subgroup variable is less than 5% of the ITT population, the subgroup analysis was not performed for this category of the subgroup variable. If there is only one category of a subgroup left (meaning other categories of a subgroup variable are all less than 5% of the ITT population), this subgroup variable was not displayed in the forest plot. Subgroup variables used in the forest plot are from the latest database (i.e., ADSL from FA).

Database Cutoff Date: 15DEC2021.

Analysis by MSI-H

MSS (Microsatellite Stable)

OS

Figure 12 Kaplan-Meier Estimates of Overall Survival (Participants with MSS, ITT population)

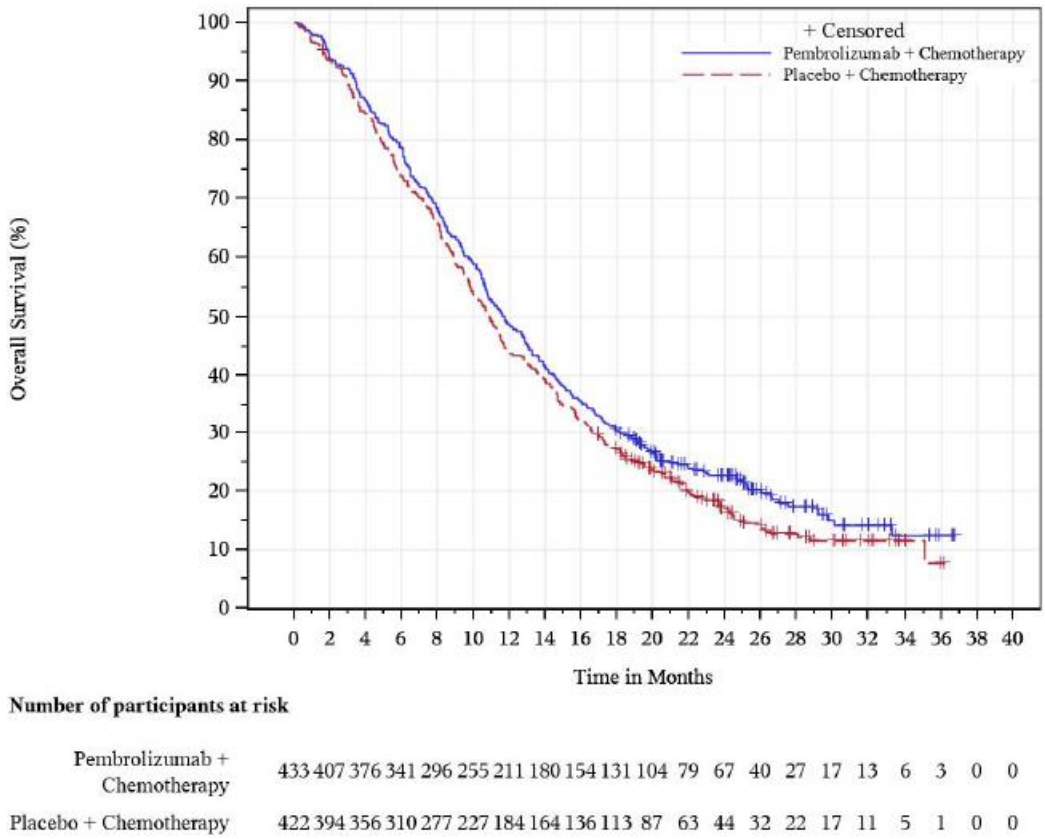


Table 28 Analysis of Overall Survival (Participants with MSS, ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	433	347 (80.1)	5841.8	5.9	11.8 (10.7, 13.0)
Placebo + Chemotherapy	422	355 (84.1)	5313.1	6.7	10.9 (9.8, 11.7)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.86 (0.74, 1.00)		0.0291[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Non-Asia), disease status (locally advanced versus metastatic), site of origin (gallbladder versus intrahepatic versus extrahepatic) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Non-Asia), disease status (locally advanced versus metastatic), site of origin (gallbladder versus intrahepatic versus extrahepatic) with small strata collapsed as pre-specified in the sSAP.
Database Cutoff Date: 15DEC2022.

Analysis by combined positive score (CPS)

CPS ≥10

OS

Table 29 Analysis of Overall Survival (Participants with PD-L1 CPS >=10, ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	203	162 (79.8)	2678.7	6.0	11.0 (10.2, 12.8)
Placebo + Chemotherapy	186	160 (86.0)	2261.5	7.1	10.3 (8.7, 11.4)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.84 (0.68, 1.05)		

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
Database Cutoff Date: 15DEC2022.

PFS

Table 30 Analysis of Progression-free Survival at FA (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (Participants with PD-L1 CPS >=10, ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	203	164 (80.8)	1464.6	11.2	5.8 (5.0, 7.2)
Placebo + Chemotherapy	186	155 (83.3)	1208.4	12.8	5.4 (4.4, 6.8)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.90 (0.72, 1.12)		

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

CPS <10

OS

Table 31 Analysis of Overall Survival (Participants with PD-L1 CPS <10, ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	273	211 (77.3)	4009.4	5.3	13.1 (11.6, 14.9)
Placebo + Chemotherapy	289	236 (81.7)	3810.3	6.2	11.6 (10.2, 13.6)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.84 (0.70, 1.01)		

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
Database Cutoff Date: 15DEC2022.

PFS

Table 32 Analysis of Progression-free Survival at FA (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (Participants with PD-L1 CPS <10, ITT population)

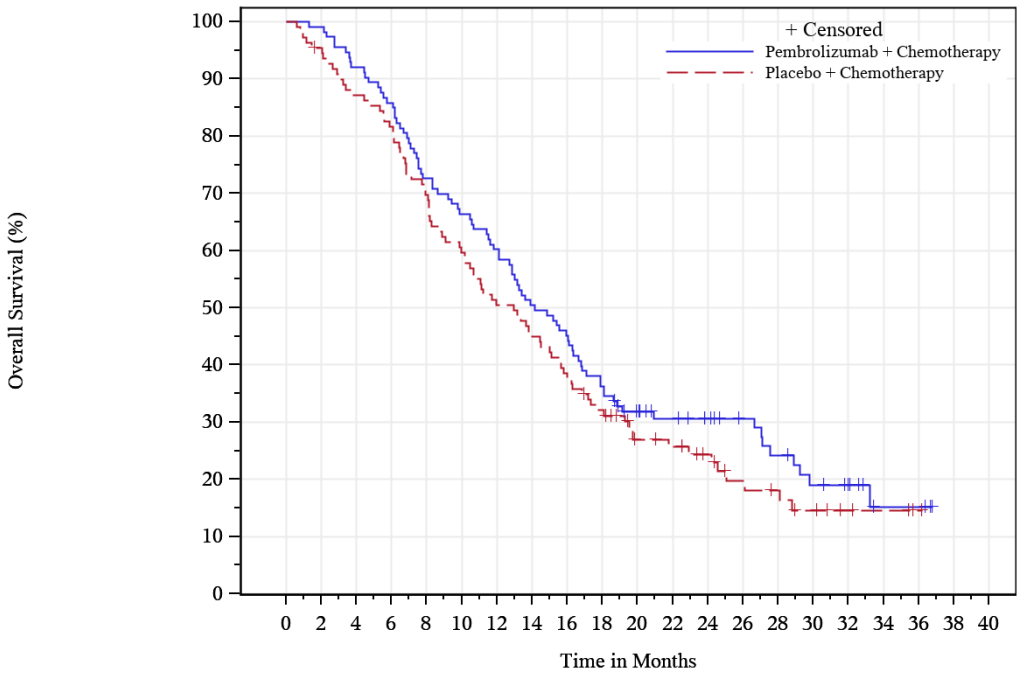
Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	273	220 (80.6)	2083.9	10.6	6.8 (5.7, 7.9)
Placebo + Chemotherapy	289	243 (84.1)	1931.2	12.6	5.7 (4.7, 6.9)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.84 (0.70, 1.01)		

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

CPS <1

OS

Figure 13 Kaplan-Meier Estimates of Overall Survival (Participants with PD-L1 CPS < 1, ITT Population)



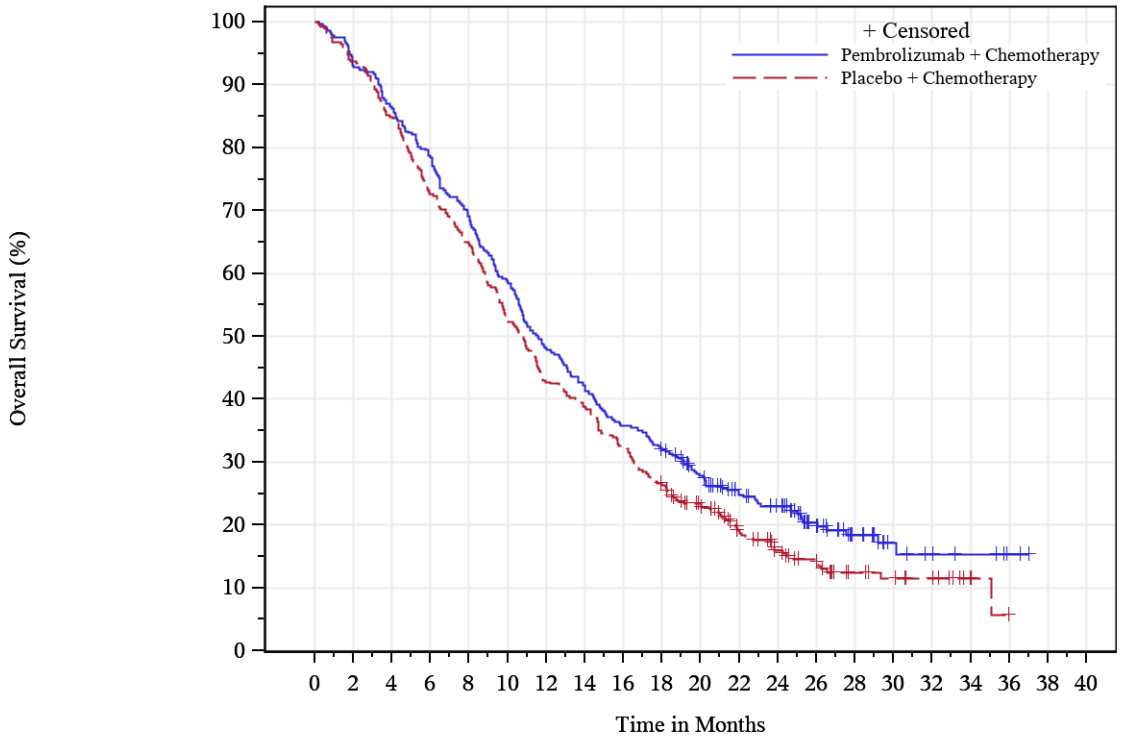
Number of participants at risk

Pembrolizumab + Chemotherapy	113	112	104	97	82	75	68	57	51	41	32	27	23	19	15	11	9	3	3	0	0
Placebo + Chemotherapy	110	104	95	89	76	65	55	49	42	34	24	22	17	12	10	7	4	3	1	0	0

CPS ≥ 1

OS

Figure 14 Kaplan-Meier Estimates of Overall Survival (Participants with PD-L1 CPS ⩾ 1, ITT Population)



Number of participants at risk

Pembrolizumab + Chemotherapy	363	338	314	286	251	213	175	152	130	115	94	71	61	36	20	10	7	5	2	0	0
Placebo + Chemotherapy	365	342	310	265	236	193	156	141	118	96	76	51	36	27	16	13	10	4	0	0	0

Analysis by Age

OS

Table 33 Analysis of Overall Survival (Age <65 Years) (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	269	210 (78.1)	3741.2	5.6	12.8 (11.6, 14.1)
Placebo + Chemotherapy	298	242 (81.2)	3853.0	6.3	10.9 (9.7, 12.0)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.88 (0.73, 1.05)		0.0790[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
Database Cutoff Date: 15DEC2022.

Table 34 Analysis of Overall Survival (Age 65-74 Years) (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	196	154 (78.6)	2845.4	5.4	13.2 (11.0, 14.6)
Placebo + Chemotherapy	181	153 (84.5)	2292.4	6.7	11.1 (9.6, 13.9)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.79 (0.63, 0.99)		0.0201[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
Database Cutoff Date: 15DEC2022.

Table 35 Analysis of Overall Survival (Age >=75 Years) (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	68	50 (73.5)	886.7	5.6	9.0 (7.9, 14.9)
Placebo + Chemotherapy	57	48 (84.2)	654.2	7.3	9.4 (6.4, 14.0)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.81 (0.54, 1.20)		0.1423[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
Database Cutoff Date: 15DEC2022.

PFS

Table 36 Analysis of Progression-free Survival at FA (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (Age <65 Years) (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	269	217 (80.7)	1845.3	11.8	6.4 (5.6, 6.9)
Placebo + Chemotherapy	298	246 (82.6)	1962.2	12.5	5.6 (5.2, 6.9)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.95 (0.79, 1.14)		0.2924[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

Table 37 Analysis of Progression-free Survival at FA (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (Age 65 – 74 Years) (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	196	152 (77.6)	1599.9	9.5	7.4 (5.7, 8.3)
Placebo + Chemotherapy	181	153 (84.5)	1173.4	13.0	5.6 (4.4, 6.9)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			0.74 (0.59, 0.93)		0.0041[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

Table 38 Analysis of Progression-free Survival at FA (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (Age >=75 Years) (ITT population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)
Pembrolizumab + Chemotherapy	68	59 (86.8)	486.6	12.1	5.5 (3.3, 7.7)
Placebo + Chemotherapy	57	49 (86.0)	396.7	12.4	4.3 (3.4, 7.2)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]		p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy			1.00 (0.68, 1.46)		0.4901[c]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

ORR

Table 39 Analysis of Objective Response with Confirmation at FA Based on BICR Assessment per RECIST 1.1 (Age <65 Years) (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Placebo + Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	269	80	29.7 (24.3, 35.6)	1.2 (-6.3, 8.7)	0.3752
Placebo + Chemotherapy	298	85	28.5 (23.5, 34.0)		

[a] Based on Miettinen & Nurminen method.
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

Table 40 Analysis of Objective Response with Confirmation at FA Based on BICR Assessment per RECIST 1.1 (Age 65-74 Years) (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Placebo + Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	196	62	31.6 (25.2, 38.6)	2.9 (-6.4, 12.1)	0.2701
Placebo + Chemotherapy	181	52	28.7 (22.3, 35.9)		

[a] Based on Miettinen & Nurminen method.
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

Table 41 Analysis of Objective Response with Confirmation at FA Based on BICR Assessment per RECIST 1.1 (Age >=75 Years) (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Placebo + Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	68	14	20.6 (11.7, 32.1)	-5.7 (-21.0, 9.1)	0.7741
Placebo + Chemotherapy	57	15	26.3 (15.5, 39.7)		

[a] Based on Miettinen & Nurminen method.
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
BICR = Blinded independent central review.
Database Cutoff Date: 15DEC2022.

Subsequent therapies

Table 42 Summary of Subsequent Oncologic Therapies (ITT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	533		536	
Participants in one or more subsequent oncologic therapies	253	(47.5)	261	(48.7)
Chemotherapy	**230**	**(43.2)**	**230**	**(42.9)**
CAPECITABINE	49	(9.2)	51	(9.5)
CAPECITABINE;OXALIPLATIN	2	(0.4)	1	(0.2)
CARBOPLATIN	6	(1.1)	4	(0.7)
CISPLATIN	50	(9.4)	56	(10.4)
CISPLATIN;GEMCITABINE	2	(0.4)	0	(0.0)
DOCETAXEL	0	(0.0)	1	(0.2)
FLUOROURACIL	126	(23.6)	127	(23.7)
GEMCITABINE	41	(7.7)	42	(7.8)
GEMCITABINE HYDROCHLORIDE	9	(1.7)	8	(1.5)
GIMERACIL;OTERACIL POTASSIUM;TEGAFUR	37	(6.9)	33	(6.2)
IRINOTECAN	45	(8.4)	42	(7.8)
IRINOTECAN HYDROCHLORIDE	8	(1.5)	12	(2.2)
IRINOTECAN HYDROCHLORIDE TRIHYDRATE LIPOSOMAL	5	(0.9)	3	(0.6)
MITOMYCIN	0	(0.0)	1	(0.2)
OXALIPLATIN	109	(20.5)	111	(20.7)
PACLITAXEL	7	(1.3)	5	(0.9)
PACLITAXEL NANOPARTICLE ALBUMIN-BOUND	14	(2.6)	15	(2.8)
PEMETREXED DISODIUM	1	(0.2)	1	(0.2)
RALTITREXED	0	(0.0)	1	(0.2)
TEGAFUR	3	(0.6)	0	(0.0)
Immune Checkpoint Inhibitors	**26**	**(4.9)**	**38**	**(7.1)**
ATEZOLIZUMAB	1	(0.2)	1	(0.2)
CAMRELIZUMAB	2	(0.4)	2	(0.4)
DURVALUMAB	3	(0.6)	4	(0.7)
ENVAFOLIMAB	1	(0.2)	1	(0.2)
IPILIMUMAB	0	(0.0)	4	(0.7)
NIVOLUMAB	8	(1.5)	18	(3.4)
PD-1/PDL-1 (PROGRAMMED CELL DEATH PROTEIN 1/DEATH LIGAND 1) INHIBITORS	1	(0.2)	0	(0.0)
PEMBROLIZUMAB	4	(0.8)	5	(0.9)
PEMBROLIZUMAB;VIBOSTOLIMAB	0	(0.0)	2	(0.4)
SINTILIMAB	3	(0.6)	3	(0.6)
SPARTALIZUMAB	1	(0.2)	0	(0.0)
TISLELIZUMAB	2	(0.4)	1	(0.2)
TORIPALIMAB	1	(0.2)	1	(0.2)
TREMELIMUMAB	0	(0.0)	3	(0.6)
Targeted Therapy	**6**	**(1.1)**	**18**	**(3.4)**
ERDAFITINIB	0	(0.0)	1	(0.2)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Targeted Therapy	**6**	**(1.1)**	**18**	**(3.4)**
FIBROBLAST GROWTH FACTOR RECEPTOR (FGFR) TYROSINE KINASE INHIBITORS	0	(0.0)	3	(0.6)
HMPL 306	0	(0.0)	2	(0.4)
INFIGRATINIB	0	(0.0)	1	(0.2)
IVOSIDENIB	4	(0.8)	3	(0.6)
PEMIGATINIB	2	(0.4)	8	(1.5)
Other	**43**	**(8.1)**	**50**	**(9.3)**
ANTINEOPLASTIC AGENTS	2	(0.4)	1	(0.2)
ASCIMINIB	0	(0.0)	1	(0.2)
BELZUTIFAN	0	(0.0)	1	(0.2)
BEVACIZUMAB	1	(0.2)	4	(0.7)
BEXMARILIMAB	1	(0.2)	0	(0.0)
BI 905711	0	(0.0)	1	(0.2)
BINIMETINIB	1	(0.2)	0	(0.0)
CATEQUENTINIB HYDROCHLORIDE	5	(0.9)	2	(0.4)
CERITINIB	0	(0.0)	1	(0.2)
CETUXIMAB	1	(0.2)	0	(0.0)
DABRAFENIB	3	(0.6)	1	(0.2)
DABRAFENIB MESILATE	0	(0.0)	1	(0.2)
DASATINIB	0	(0.0)	1	(0.2)
DONAFENIB	1	(0.2)	1	(0.2)
ENCORAFENIB	1	(0.2)	0	(0.0)
ERLOTINIB HYDROCHLORIDE	2	(0.4)	1	(0.2)
FRUQUINTINIB	1	(0.2)	0	(0.0)
IMATINIB MESILATE	0	(0.0)	1	(0.2)
INVESTIGATIONAL DRUG	3	(0.6)	2	(0.4)
LENVATINIB	5	(0.9)	8	(1.5)
LENVATINIB MESILATE	7	(1.3)	4	(0.7)
LY 3410738	0	(0.0)	1	(0.2)
OLAPARIB	0	(0.0)	1	(0.2)
OTHER ANTINEOPLASTIC AGENTS	2	(0.4)	0	(0.0)
OTHER IMMUNOSTIMULANTS	0	(0.0)	1	(0.2)
OTHER MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES	2	(0.4)	2	(0.4)
OTHER PROTEIN KINASE INHIBITORS	1	(0.2)	1	(0.2)
OTHER THERAPEUTIC PRODUCTS	1	(0.2)	1	(0.2)
PALBOCICLIB	1	(0.2)	0	(0.0)
PERTUZUMAB	1	(0.2)	3	(0.6)
REGORAFENIB	1	(0.2)	2	(0.4)
RIVOCERANIB	0	(0.0)	2	(0.4)
RIVOCERANIB MESYLATE	1	(0.2)	1	(0.2)
RXC 004	1	(0.2)	0	(0.0)
SURUFATINIB	1	(0.2)	0	(0.0)
TNO 155	1	(0.2)	0	(0.0)
TRAMETINIB	3	(0.6)	4	(0.7)
TRASTUZUMAB	3	(0.6)	7	(1.3)
TRASTUZUMAB ANNS	0	(0.0)	1	(0.2)
TRASTUZUMAB DERUXTECAN NXKI	0	(0.0)	1	(0.2)
TUCATINIB	0	(0.0)	1	(0.2)

Every participant is counted a single time for each applicable specific oncologic treatment. A participant with multiple oncologic treatment within a medication category is counted a single time for that category.
WHO-DD GLOBALB3Sep22 was used in the reporting of this study.
Database Cutoff Date: 15DEC2022.

Table 43 Subsequent local therapies for liver disease after PD (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	533		536	
Surgery	**1**	**(0.2)**	**0**	**(0.0)**
Radiotherapy	**2**	**(0.4)**	**6**	**(1.1)**
Locoregional therapy	**3**	**(0.6)**	**6**	**(1.1)**
Database Cutoff Date: 15DEC2022.				

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44 Summary of Efficacy for trial KEYNOTE-966

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 identifier	IND: 123482; EudraCT: 2019-000944-82		
Design	Phase 3, randomized, double-blind, placebo-controlled		
Hypothesis	Superiority		
Treatments groups	Pembrolizumab + Chemotherapy		Pembrolizumab 200 mg Day 1 of each cycle, up to 35 administrations + gemcitabine 1000 mg/m2, Day 1 and Day 8 of each cycle, until PD or unacceptable toxicity + cisplatin 25 mg/m2 Day 1 and Day 8 of each cycle, up to 8 cycles number randomized: 533
	Placebo + Chemotherapy		Placebo Day 1 of each cycle, up to 35 administrations + gemcitabine 1000 mg/m2, Day 1 and Day 8 of each cycle, until PD or unacceptable toxicity + cisplatin 25 mg/m2 Day 1 and Day 8 of each cycle, up to 8 cycles number randomized: 536
Endpoints and definitions	Primary endpoint	OS	Time from randomization to death due to any cause
	Secondary endpoint	PFS	Time from randomization to PD, based upon RECIST 1.1 by BICR or death, whichever occurred earlier
	Secondary endpoint	ORR	proportion of subjects who have a confirmed CR or PR by BICR
		DoR	time from first documented evidence of CR or PR until disease progression or death
Database cut off	15-DEC-2022 (FA)		
Database lock	19-JAN-2023 (FA)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy
	Number of subject	533	536
	OS (median months)	12.7	10.9
	95% CI	11.5, 13.6	9.9, 11.6
	PFS (median months)	6.5	5.6
	95% CI	5.7, 6.9	5.1, 6.6
	ORR (CR+PR) (%)	28.7	28.5
	DOR (median months)	9.7 (1.2+ - 22.7+)	6.9 (0.0+ - 19.2+)
Effect estimate per comparison	Primary endpoint	Pembrolizumab+chemotherapy vs placebo+chemotherapy	**OS**
		HR	0.83
		95% CI	(0.72, 0.95)
		P-value	0.0034
	Secondary endpoint	Pembrolizumab+chemotherapy vs placebo+chemotherapy	**PFS**
		HR	0.86
		95% CI	0.75, 1.00
		P-value	0.0225
Notes	Primary efficacy endpoint of OS was analysed at FA (DCO for FA is 15-DEC-2022). The analyses of PFS, ORR, and DOR (secondary endpoints) were prespecified in the protocol to be based on IA1 data (15-DEC-2021 DCO)		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

KEYNOTE-966 was a superiority trial designed to demonstrate advantage of pembrolizumab in association with gemcitabine plus cisplatin over duplex chemotherapy alone as first-line therapy in patients with locally advanced (unresectable) or metastatic BTC (intra- or extrahepatic cholangiocarcinoma or gallbladder).

Based on the **inclusion/exclusion** criteria, a broad population in terms of cancer site and hepatitis status was eligible for recruitment, although limited to relatively fit patients (PS 0-1). Histologically confirmed diagnosis of BTC was requested. Exposure to prior systemic therapies was an exclusion criterion, with the exception of neo-adjuvant/adjuvant treatments not containing gemcitabine and/or cisplatin. Participants who received prior neoadjuvant/adjuvant therapy with R2 resection were excluded. Overall, the study population can be considered representative of the advanced/metastatic BTC setting.

Pembrolizumab was tested at a **dose** of 200 mg IV Q3W, in line with the licensed posology for KEYTRUDA as monotherapy and combination with chemotherapy. Pembrolizumab was administrated on top of a backbone therapy with gemcitabine plus cisplatin. The chemotherapeutic scheme adopted in KEYNOTE-966 can be considered standard and in line with current clinical recommendations. The association of gemcitabine and cisplatin represents the most common front-line approach in BTC patients, although other gemcitabine-based regimens are available. However, the study population recruited in KEYNOTE-966 does not provide representativeness of alternative chemotherapeutic schemes generally used in *cisplatin-unfit* patients carrying a worse prognosis and reduced effect of therapies; moreover, the tolerability in association with pembrolizumab cannot be predicted in this more frail subgroup that have

not been included in the pivotal trial. The wording in section 4.1 of the SmPC was revised to clearly reflect the tested chemotherapeutic agents adopted in the pivotal trial: *KEYTRUDA, in combination with ~~gemcitabine-based chemotherapy~~* ***gemcitabine and cisplatin****, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults*.

The **primary endpoint** was OS, which is endorsed in an aggressive disease setting such as BTC. **Secondary endpoints** include PFS per RECIST 1.1, ORR (CR or PR) and DoR as assessed by BICR, which are also supported for the efficacy evaluation. Among **tertiary endpoints**, PFS, ORR and DoR as evaluated by Investigators, disease control (DC) rate, time-to-deterioration (TTT) and Quality of Life (QOL) questionnaires, are considered adequate. Efficacy by PD-L1 status (CPS $\geqslant$1 versus <1, and additional cutoff $\geqslant$10) was not pre-specified but rather included in the exploratory outcomes. The primary efficacy endpoint of OS was analysed at FA. The PFS, ORR, and DOR (secondary endpoints) were prespecified in the protocol to be evaluated on the basis of IA1 data (15 DEC-2021 data cutoff). The median time from randomization to DCO in the ITT population was 25.6 months (range 18.3 to 38.4 months) for the FA and 13.6 months (range 6.3 to 26.4 months) for the IA1.

Approximately 1048 participants were expected to be randomized 1:1 into pembrolizumab plus gemcitabine plus cisplatin or placebo plus gemcitabine plus cisplatin. After the enrollment of the global portion was complete, the study remained open to enrolment in China alone for the China extension cohort of 46 participants until a total of 158 participants had been enrolled across the global and extension parts to meet local regulatory requirements in China. This report describes the global portion of the study. The **sample size** calculation is comprehensible and reproducible. Of the six amendments to the protocol, only amendment 2 (08-DEC-2020) affected the sample size and power calculation; the sample size was increased from the initial 788 to 1048 participants to maintain study timelines and statistical power. The final number of randomized participants was 1069.

The ITT population served as the population for the primary efficacy analyses of OS. All randomly assigned participants were included in this population. The efficacy analyses of OS in this submission were based on FA (DCO 15-DEC-2022), which was the third analysis of OS. At the FA data cut-off, descriptive analyses for key secondary endpoints of PFS and ORR were provided since the final analyses for these endpoints were performed at IA1 (DCO 15-DEC-2021).

Statistical methods were well reported in the protocol section and in the Amendment 04 of supplemental SAP (sSAP) dated 13-JUN-2022, which represents its latest version. Overall, statistical methods are considered appropriate: the overall type I error over the primary endpoints (OS) and the key secondary endpoint (PFS and ORR) is strongly controlled at 2.5% (one-sided), with initially 2.5% allocated to OS (H1); by using the graphical approach of Mauer and Bretz if OS hypothesis was rejected, the corresponding alpha was reallocated equally to PFS and ORR; if the PFS hypothesis was rejected, the corresponding alpha was reallocated to ORR; if the ORR hypothesis was rejected, the corresponding alpha was reallocated to PFS.

There were six **protocol amendments** over the study course, among these only amendments 2, 4 and 5 affected the SAP language. Amendment 2 (08-DEC-2020) brought the most significant changes, since the primary endpoints of the study were modified, a more conservative hazard ratio assumption for OS was made accounting for possible delayed treatment effect and, consequently, the sample size was increased from the initial 788 to 1048 participants, in order to maintain study timelines and statistical power. The rationale for these amendments was exhaustively explained.

Important **protocol deviations** were within acceptable limits (8.9%); the most frequently reported reason among those considered of clinical relevance (2.8%), was the improper storage of study drug (1.4%). One case of serious GCP breach without safety impact was reported, due to the use of incorrect ALT reference ranges that caused the erroneous recruitment of a patient not meeting the eligibility criteria. Overall, no concerns arise as regards the conduct of the study.

Sensitivity analyses were adequate.

Efficacy data and additional analyses

The current application is based on the FA (DCO: 15-DEC-2022) of study KEYNOTE-966 for the primary endpoint OS, while secondary endpoints were formally tested at IA1 (DCO: 15-DEC-2021) although descriptive statistics were provided at the final analysis.

As of the data cutoff for FA (15-DEC-2022), 1564 subjects were screened with 1069 being randomized (533 to pembrolizumab plus gemcitabine/cisplatin and 536 to placebo plus gemcitabine plus cisplatin), while 495 (31.6%) non-randomized participants were **screen failures** since they did not meet all inclusion/exclusion criteria. A total of 6 participants (pembrolizumab arm: 4; placebo arm: 2) were randomized but did not receive the study treatment. The screen failure rate was higher than expected, mostly associated with inappropriate organ function (haematological, renal and liver) as defined by the inclusion criteria. Concomitant disease-associated liver dysfunction at baseline was the main reason for screen failure in KEYNOTE-966, as it was for the TOPAZ-1 trial testing durvalumab combination in the same indication. It is common practice that gemcitabine administration in patients with liver dysfunction needs to be carefully monitored due to the anticipated liver toxicity that in a combination therapy is expected to increase. Yet, treatment with gemcitabine-based chemotherapy is not contraindicated in the presence of liver dysfunction and there is a wide experience with the use of chemotherapy in this clinical setting. A specification of liver function of patients enrolled in KEYNOTE-966 (serum bilirubin levels ($\leqslant$1.5 x ULN or direct bilirubin $\leqslant$ ULN for participants with total bilirubin levels > 1.5 $\times$ ULN) and resolved clinically significant biliary obstruction) as defined in the protocol has been reported in section 5.1 of the SmPC for an appropriate information to treating physicians.

At the time of FA (15-DEC-2022) median time to data cut-off was of 25.6 months (range: 18.3; 38.4), with a median follow-up of 12.7 (range: 0.2; 37.5) and 10.9 (range: 0.2; 36.2) months in the experimental and control arm, respectively. In total, 857 OS events over 818 required were observed (414 in pembrolizumab + chemotherapy arm and 443 in placebo + chemotherapy arm), based on which the study can be considered mature.

The 80.4% of the population underwent **discontinuation** from the trial, (77.7% vs 83.2% in the pembrolizumab and placebo group, respectively), the main reason being death in both treatment groups (76.7% vs 82.6%). Discontinuation from study medication was registered in 93.4% of participants, occurring at an almost equal rate in both arms (92.4% vs 94.4 in the pembrolizumab and placebo group, respectively). Progressive disease was the most common reason (61.2% and 66.3% in the pembrolizumab and placebo group, respectively) while adverse events contributed to only a minority of cases (12.7% vs 11.4% in the pembrolizumab and placebo group, respectively). At the time of FA, treatment was ongoing in 4.7% of the ITT (5.1% vs 4.3% in the pembrolizumab and placebo, respectively).

Baseline and disease characteristics were well balanced between groups. In the recruited population, there was a slight predominance of male patients (51.6% vs 48.4% for female sex), age was 64.0 years in median. Asians and non-Asians were almost equally represented, but Western Europe was a minority (28.3%) among regions, with a dominance of Rest of the World (63.8%). The prevailing tumour site was intrahepatic (59.2%) compared to the gallbladder (21.8%) and extrahepatic location (19%). Metastatic was more frequent than advanced disease (88.2% vs 11.8%, respectively). No major differences could be observed between treatment arms in the anatomical distribution of metastases. Liver (58.9% and 56%) and lymph nodes (58.2% and 54.7%) were the prevailing sites in both groups, followed by respiratory (29.8% and 27.2%) and peritoneum (24.4% and 24.3%). Other locations were also similarly affected, with the exception of a slightly higher prevalence of metastases in the abdomen cavity wall and organs

(other than liver) in the placebo group (7.9% and 10.6%).All these baseline characteristics are expected according with the disease epidemiology. Patients were almost all HCV negative (96.7%) with only a minority having a prior HCV infection (2.9%); the majority of the population was HBV negative (68.5%), 28% had a clinically resolved prior infection and 2.8% a chronic HBV infection. In terms of tumour hallmarks, the PDL-1 status was similar between groups, with a higher frequency of CPS≥1 (68.1%) than CPS<1 (20.9%); in a not negligible portion of tumours, CPS remained indeterminate (11%). At the MSI characterisation, the majority of the population was MSS (80%; it was indeterminate in 19.1%). Overall, the study population can be considered representative of the whole target population.

Pembrolizumab, in addition to gemcitabine+cisplatin, provided advantage compared to gemcitabine+cisplatin alone on the **primary endpoint** OS (HR=0.83; 95% CI: 0.72; 0.95; p=0.0034), with a gain in median survival of 1.8 months (12.7 vs 10.9). These results are similar to the magnitude of effect that was reported for durvalumab on top of gemcitabine+cisplatin in the TOPAZ-1 trial (HR= 0.80; 95% CI: 0.66, 0.97; p-value 0.021; median OS gain ~1.5 months) (see Imfinzi SmPC).

The **secondary endpoint** PFS did not meet statistically significance. It showed a trend towards improvement in the experimental vs the control arm (HR=0.86; 95% CI: 0.75,1; p=0.0225) at IA1, that was confirmed at the FA (HR=0.87; 95% CI: 0.76, 0.99; p=0.0171). The ORR was unchanged by pembrolizumab treatment (28.7% vs 28.5% in the pembrolizumab and placebo arm, respectively at IA1; 29.3% vs 28.4% in the pembrolizumab and placebo arm, respectively at FA), although a slightly longer duration of response was registered in the experimental arm compared to control (9.7 vs 6.9 months at IA1; 8.3 vs 6.8 months at FA).

Among **exploratory endpoints**, PROs were comparable between arms.

Subgroup analysis demonstrated consistency across the main prespecified subgroups, with the exception of a lower performance of pembrolizumab in OS for the gallbladder (HR=0.96; 95% CI:0.73, 1.26) and extrahepatic (HR=0.99; 95% CI:0.73,1.35) tumour, compared to the intrahepatic cancer (HR=0.76; 95% CI:0.64,0.91). A similar behaviour was reported for durvalumab in the TOPAZ-1 trial. The PFS and ORR followed the same trend, with the PFS reaching a HR>1 in the extrahepatic localisation, and ORR showing even disadvantage of pembrolizumab vs placebo in the extrahepatic and gallbladder cancer sites. Due to the availability of limited clinical data and poor knowledge around peculiarities in biological/clinical features that might impact response to immunomodulators, no firm conclusions can be derived on the reasons and biological plausibility underlying inconsistency in treatment effect across tumour locations. Considering the absence of a detrimental effect in these subgroups on the basis of the survival primary endpoint, it can be concluded that a positive B/R of pembrolizumab in association to chemotherapy applies regardless of anatomical classification.

The efficacy evaluation by **CPS** score, either by using 1 or 10 as cut-off point, demonstrated similar results in the different subgroups regardless of the PD-L1 status.

OS and PFS were consistent in **Asians and non-Asians**, although ORR was enhanced by pembrolizumab in Asians (difference between pembrolizumab and placebo of 4) but reduced by treatment in non-Asians (difference between pembrolizumab and placebo of -3). The TOPAZ-1 trial reported increased efficacy of durvalumab in countries known to be fluke-endemic compared to the ITT population. This pattern was not replicated in KEYNOTE-966, where response to treatment was even more attenuated in this geographically determined subgroup (HR=0.92; 95% CI: 0.72;1.17) compared to the overall population, though not indicative of a clear detrimental effect. The OS by hepatitis status was generally consistent with the treatment performance registered in the overall population.

Efficacy by **age** was generally comparable in the different patient categories, in terms of OS and PFS. However, the ORR was reduced by pembrolizumab relative to placebo in patients aged ≥75 years compared to the youngest population (9.0 vs 9.4 for pembrolizumab plus chemotherapy and placebo plus

chemotherapy, respectively). No clear signs of detrimental effect emerged in the oldest. In any case, a warning for the use of pembrolizumab in the elderly population, particularly in combination with chemotherapy, is already included in the SmPC as a general consideration, which also applies to the current clinical setting (see SmPC section 4.4).

There were no substantial differences in the list of **subsequent therapies** between groups, since cytotoxic agents were equally received by patients (43.2% vs 42.9% in the pembrolizumab vs placebo arm) with a prevailing use of the FOLFOX regimen (>20% in both arms); as expected, a slightly more frequent administration of checkpoint inhibitors was reported in the placebo arm (7.1% vs 4.9% in the pembrolizumab arm). The use of localised therapy after disease progression was very limited in the study population (0.2-1.1%), overall balanced between treatment arms.

2.4.4. Conclusions on the clinical efficacy

Overall, the efficacy evaluation supported a modest survival advantage of pembrolizumab versus placebo on top of gemcitabicine plus cisplatin in the first-line treatment of the advanced BTC disease setting. The final indication wording was updated to clearly reflect that the backbone therapy used was gemcitabine plus cisplatin.

2.5. Clinical safety

Introduction

KEYNOTE-966 is an ongoing Phase 3, randomized, double-blind study of pembrolizumab plus chemotherapy versus placebo plus chemotherapy in participants with locally advanced unresectable or metastatic biliary tract carcinoma. Safety analyses used the All Participants as Treated (APaT) population of all participants who received at least 1 dose of study intervention, as of the FA DCO date of 15-DEC-2022. Pooled safety data from studies of pembrolizumab in combination with chemotherapy in NSCLC (KEYNOTE-021 Cohorts A, C, and G, KEYNOTE-189, and KEYNOTE-407), HNSCC (KEYNOTE-048), TNBC (KEYNOTE-355), and esophageal carcinoma (KEYNOTE-590) are included to provide a point of reference on the safety profile of pembrolizumab in combination with chemotherapy. Participants in the Pooled Combination Dataset received pembrolizumab along with one or more chemotherapeutic agents. These chemotherapies included platinum-based chemotherapy, 5-fluorouracil, paclitaxel/nab-paclitaxel, gemcitabine, and pemetrexed. The safety results are presented for the following 4 datasets (see table below):

Table 45 Safety Datasets and Treatment Group Nomenclature

Dataset	**Population**	**Nomenclature in Tables**	**Nomenclature in Text**
KEYNOTE-966 pembrolizumab plus chemotherapy (gemcitabine plus cisplatin)	(N=529): Participants from KEYNOTE-966 who received at least 1 dose of pembrolizumab in combination with chemotherapy in KEYNOTE-966	KN966 Pembrolizumab + Chemotherapy	pembrolizumab plus chemotherapy group
KEYNOTE-966 placebo plus chemotherapy	(N=534): Participants from KEYNOTE-966 who received at least 1 dose of placebo in combination with chemotherapy in KEYNOTE-966	KN966 Placebo + Chemotherapy	placebo plus chemotherapy group

(gemcitabine plus cisplatin)			
Pembrolizumab plus chemotherapy	(N=2,033): Pooled safety data from participants treated with pembrolizumab plus platinum-based chemotherapy, including 791 participants with NSCLC from KEYNOTE-021, KEYNOTE-189, KEYNOTE-407, 276 participants with HNSCC from KEYNOTE-048, 370 participants with esophageal cancer from KEYNOTE-590, and 596 participants with TNBC from KEYNOTE-355	Pooled Safety Dataset for Pembrolizumab + Chemotherapy	Pooled Combination Dataset
Pembrolizumab monotherapy reference safety	(N=7,631): Pooled safety data from participants treated with pembrolizumab monotherapy, including 2559 participants with advanced melanoma from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-054, and KEYNOTE-716; 2022 participants with NSCLC from KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042; 909 participants with HNSCC from KEYNOTE-012, KEYNOTE-040, KEYNOTE-048, and KEYNOTE-055; 636 participants with bladder cancer from KEYNOTE-045, and KEYNOTE-052; 488 participants with RCC from KEYNOTE-564; 475 participants with MSI-H tumors from KEYNOTE-158 and KEYNOTE-164; 389 participants with HL from KEYNOTE-013, KEYNOTE-087, and KEYNOTE-204; 153 participants with MSI-H CRC from KEYNOTE-177.	RSD for Pembrolizumab	RSD
Abbreviations: CRC=colorectal cancer; HL= Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; MSI-H=microsatellite instability-high; N=number; NSCLC=non-small cell lung cancer; RCC=renal cell carcinoma; RSD=reference safety dataset; TNBC=triple-negative breast cancer.			

Table 46 Participant characteristics (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
Sex								
Male	279	(52.7)	270	(50.6)	1,041	(51.2)	4,889	(64.1)
Female	250	(47.3)	264	(49.4)	992	(48.8)	2,742	(35.9)
Age (Years)								
<65	266	(50.3)	296	(55.4)	1,218	(59.9)	4,524	(59.3)
>=65	263	(49.7)	238	(44.6)	815	(40.1)	3,107	(40.7)
Mean	63.3		61.9		60.2		59.9	
SD	10.3		11.0		11.4		13.4	

Median	64.0		63.0		62.0		62.0	
Range	23 to 85		28 to 84		20 to 94		15 to 94	
Race								
American Indian Or Alaska Native	2	(0.4)	1	(0.2)	23	(1.1)	59	(0.8)
Asian	243	(45.9)	249	(46.6)	472	(23.2)	826	(10.8)
Black Or African American	11	(2.1)	3	(0.6)	66	(3.2)	146	(1.9)
Multiracial	5	(0.9)	2	(0.4)	19	(0.9)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	0	(0.0)	1	(0.0)	5	(0.1)
White	254	(48.0)	267	(50.0)	1,416	(69.7)	5,838	(76.5)
Missing	13	(2.5)	12	(2.2)	36	(1.8)	671	(8.8)
Ethnicity								
Hispanic Or Latino	58	(11.0)	52	(9.7)	235	(11.6)	604	(7.9)
Not Hispanic Or Latino	431	(81.5)	447	(83.7)	1,695	(83.4)	6,064	(79.5)
Not Reported	31	(5.9)	31	(5.8)	54	(2.7)	808	(10.6)
Unknown	5	(0.9)	3	(0.6)	46	(2.3)	145	(1.9)
Missing	4	(0.8)	1	(0.2)	3	(0.1)	10	(0.1)
Age Category (year)								
<65	266	(50.3)	296	(55.4)	1,218	(59.9)	4,524	(59.3)
65-74	195	(36.9)	181	(33.9)	653	(32.1)	2,173	(28.5)
75-84	67	(12.7)	57	(10.7)	157	(7.7)	824	(10.8)
>=85	1	(0.2)	0	(0.0)	5	(0.2)	110	(1.4)
ECOG Performance Status								
[0] Normal Activity	257	(48.6)	226	(42.3)	913	(44.9)	4,016	(52.6)
[1] Symptoms, but ambulatory	271	(51.2)	308	(57.7)	1,116	(54.9)	3,440	(45.1)
Other/Missing	1	(0.2)	0	(0.0)	4	(0.2)	175	(2.3)
Geographic Region								
North America	45	(8.5)	40	(7.5)	431	(21.2)	2,669	(35.0)
Western Europe	150	(28.4)	150	(28.1)	690	(33.9)	2,856	(37.4)
Rest of the World	334	(63.1)	344	(64.4)	912	(44.9)	2,106	(27.6)

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Patient exposure

Table 47 Drug Exposure Summary (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d] (N=529)	KN966 Placebo + Chemotherapy[d] (N=534)	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f] (N=2033)	Pembrolizumab Monotherapy Reference Safety Dataset[e] (N=7631)
Duration of Exposure (month)				
Mean	8.04	7.29	9.02	7.85
Median	6.37	5.54	6.28	5.78
SD	6.868	6.319	7.802	6.907
Range	0.03 to 36.40	0.03 to 30.62	0.03 to 48.00	0.03 to 38.01
Number of Administrations				
Mean	20.35	18.89	NA	12.33
Median	16.00	16.00	NA	9.00
SD	16.276	15.474	NA	10.116
Range	1.00 to 102.00	1.00 to 80.00	NA	1.00 to 59.00

Duration of exposure is the time from the first dose date to the last dose date.

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Table 48 Exposure by duration (APaT population)

	KN966 Pembrolizumab + Chemotherapy[d] (N=529)			KN966 Placebo + Chemotherapy[d] (N=534)			Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f] (N=2033)			Pembrolizumab Monotherapy Reference Safety Dataset[e] (N=7631)		
	n	(%)	Person-months	n	(%)	Person-months	n	(%)	Person-months	n	(%)	Person-months
Duration of Exposure (month)												
> 0	529	(100.0)	4,252.6	534	(100.0)	3,895.0	2,033	(100.0)	18,344.0	7,631	(100.0)	59,940.3
≥ 1	471	(89.0)	4,226.9	480	(89.9)	3,871.9	1,846	(90.8)	18,268.7	6,637	(87.0)	59,548.3
≥ 3	388	(73.3)	4,056.6	374	(70.0)	3,659.9	1,562	(76.8)	17,678.4	5,023	(65.8)	56,316.8
≥ 6	274	(51.8)	3,549.7	249	(46.6)	3,089.3	1,068	(52.5)	15,460.9	3,781	(49.5)	50,879.4
≥ 12	117	(22.1)	2,193.4	105	(19.7)	1,896.9	550	(27.1)	11,085.6	1,673	(21.9)	30,706.1

Each participant is counted once on each applicable duration category row.

Duration of exposure is the time from the first dose date to the last dose date.

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407- NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Adverse events

Table 49 Adverse Event Summary (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
with one or more adverse events	524	(99.1)	532	(99.6)	2,015	(99.1)	7,375	(96.6)
with no adverse event	5	(0.9)	2	(0.4)	18	(0.9)	256	(3.4)
with drug-related[a] adverse events	493	(93.2)	500	(93.6)	1,948	(95.8)	5,462	(71.6)
with toxicity grade 3-5 adverse events	451	(85.3)	449	(84.1)	1,583	(77.9)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	377	(71.3)	370	(69.3)	1,285	(63.2)	1,208	(15.8)
with serious adverse events	276	(52.2)	263	(49.3)	962	(47.3)	2,742	(35.9)
with serious drug-related adverse events	121	(22.9)	84	(15.7)	550	(27.1)	840	(11.0)
who died	31	(5.9)	49	(9.2)	139	(6.8)	346	(4.5)
who died due to a drug-related adverse event	8	(1.5)	3	(0.6)	43	(2.1)	42	(0.6)
discontinued any drug due to an adverse event	138	(26.1)	122	(22.8)	551	(27.1)	1,066	(14.0)
discontinued pembrolizumab or placebo	77	(14.6)	66	(12.4)	345	(17.0)	1,066	(14.0)
discontinued any chemotherapy	124	(23.4)	113	(21.2)	424	(20.9)	0	(0.0)
discontinued any drug due to a drug-related adverse event	102	(19.3)	81	(15.2)	434	(21.3)	639	(8.4)
discontinued pembrolizumab or placebo	47	(8.9)	26	(4.9)	234	(11.5)	639	(8.4)
discontinued any chemotherapy	90	(17.0)	73	(13.7)	334	(16.4)	0	(0.0)
discontinued any drug due to a serious adverse event	76	(14.4)	61	(11.4)	327	(16.1)	714	(9.4)
discontinued pembrolizumab or placebo	61	(11.5)	54	(10.1)	268	(13.2)	714	(9.4)
discontinued any chemotherapy	67	(12.7)	52	(9.7)	228	(11.2)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	41	(7.8)	20	(3.7)	220	(10.8)	347	(4.5)
discontinued pembrolizumab or placebo	32	(6.0)	14	(2.6)	167	(8.2)	347	(4.5)
discontinued any chemotherapy	35	(6.6)	17	(3.2)	148	(7.3)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03, with the exception of KN966 (version 5.0)

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Table 50 Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN966 Pembrolizumab + Chemotherapy[d]	KN966 Placebo + Chemotherapy[d]	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Number of Participants exposed	529	534	2033	7631
Total exposure[b] in person-months	4757.41	4405.50	20266.55	66840.89
Total events (rate)				
adverse events	10282 (216.13)	10031 (227.69)	40308 (198.89)	77451 (115.87)
drug-related[c] adverse events	6434 (135.24)	6046 (137.24)	23303 (114.98)	24852 (37.18)
toxicity grade 3-5 adverse events	2066 (43.43)	2012 (45.67)	6238 (30.78)	7376 (11.04)
toxicity grade 3-5 drug-related adverse events	1450 (30.48)	1350 (30.64)	4288 (21.16)	1760 (2.63)
serious adverse events	556 (11.69)	506 (11.49)	1939 (9.57)	4796 (7.18)
serious drug-related adverse events	172 (3.62)	118 (2.68)	887 (4.38)	1117 (1.67)
adverse events leading to death	31 (0.65)	49 (1.11)	143 (0.71)	353 (0.53)
drug-related adverse events leading to death	8 (0.17)	3 (0.07)	43 (0.21)	42 (0.06)
adverse events resulting in drug discontinuation	163 (3.43)	140 (3.18)	656 (3.24)	1149 (1.72)
drug-related adverse events resulting in drug discontinuation	124 (2.61)	92 (2.09)	515 (2.54)	699 (1.05)
serious adverse events resulting in drug discontinuation	78 (1.64)	63 (1.43)	363 (1.79)	746 (1.12)
serious drug-related adverse events resulting in drug discontinuation	43 (0.90)	21 (0.48)	242 (1.19)	362 (0.54)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.
[b] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[c] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.03, with the exception of KN966 (version 5.0)
[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.
[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.
[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407- NSCLC: 09MAY2019)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)
Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)
Database cutoff date for RCC (KN564-RCC: 14JUN2021)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for HBC (KN966: 15DEC2022)

Table 51 Participants With Adverse Events by Decreasing Incidence (Incidence ⩾ 10% in One or More Treatment Groups) (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
with one or more adverse events	524	(99.1)	532	(99.6)	2,015	(99.1)	7,375	(96.6)
with no adverse events	5	(0.9)	2	(0.4)	18	(0.9)	256	(3.4)
Neutrophil count decreased	330	(62.4)	327	(61.2)	374	(18.4)	53	(0.7)
Anaemia	323	(61.1)	313	(58.6)	1,053	(51.8)	982	(12.9)
Nausea	233	(44.0)	246	(46.1)	1,051	(51.7)	1,534	(20.1)
Platelet count decreased	211	(39.9)	212	(39.7)	250	(12.3)	95	(1.2)
Fatigue	187	(35.3)	172	(32.2)	744	(36.6)	2,368	(31.0)
Constipation	186	(35.2)	190	(35.6)	692	(34.0)	1,179	(15.5)
Decreased appetite	144	(27.2)	155	(29.0)	611	(30.1)	1,312	(17.2)
White blood cell count decreased	141	(26.7)	127	(23.8)	314	(15.4)	70	(0.9)

Pyrexia	139	(26.3)	104	(19.5)	354	(17.4)	934	(12.2)
Vomiting	122	(23.1)	128	(24.0)	560	(27.5)	945	(12.4)
Diarrhoea	103	(19.5)	98	(18.4)	644	(31.7)	1,678	(22.0)
Abdominal pain	92	(17.4)	122	(22.8)	161	(7.9)	674	(8.8)
Rash	90	(17.0)	49	(9.2)	363	(17.9)	1,175	(15.4)
Aspartate aminotransferase increased	88	(16.6)	98	(18.4)	269	(13.2)	538	(7.1)
Alanine aminotransferase increased	87	(16.4)	113	(21.2)	283	(13.9)	572	(7.5)
Hypomagnesaemia	79	(14.9)	79	(14.8)	165	(8.1)	184	(2.4)
Pruritus	77	(14.6)	51	(9.6)	283	(13.9)	1,435	(18.8)
Asthenia	75	(14.2)	95	(17.8)	379	(18.6)	880	(11.5)
Oedema peripheral	73	(13.8)	85	(15.9)	251	(12.3)	630	(8.3)
Blood creatinine increased	57	(10.8)	58	(10.9)	241	(11.9)	358	(4.7)
Alopecia	55	(10.4)	68	(12.7)	449	(22.1)	118	(1.5)
Back pain	54	(10.2)	73	(13.7)	228	(11.2)	847	(11.1)
Dyspnoea	53	(10.0)	55	(10.3)	306	(15.1)	1,130	(14.8)
Headache	53	(10.0)	46	(8.6)	290	(14.3)	946	(12.4)
Weight decreased	51	(9.6)	63	(11.8)	275	(13.5)	628	(8.2)
Blood bilirubin increased	50	(9.5)	65	(12.2)	31	(1.5)	163	(2.1)
Hypokalaemia	48	(9.1)	67	(12.5)	216	(10.6)	324	(4.2)
Hypothyroidism	46	(8.7)	14	(2.6)	260	(12.8)	937	(12.3)
Insomnia	41	(7.8)	41	(7.7)	206	(10.1)	528	(6.9)
Abdominal pain upper	40	(7.6)	57	(10.7)	126	(6.2)	298	(3.9)
Arthralgia	39	(7.4)	41	(7.7)	355	(17.5)	1,436	(18.8)
Cough	36	(6.8)	37	(6.9)	426	(21.0)	1,392	(18.2)
Dyspepsia	33	(6.2)	55	(10.3)	108	(5.3)	225	(2.9)
Dizziness	32	(6.0)	50	(9.4)	224	(11.0)	564	(7.4)
Mucosal inflammation	28	(5.3)	23	(4.3)	230	(11.3)	111	(1.5)
Leukopenia	26	(4.9)	15	(2.8)	229	(11.3)	52	(0.7)
Stomatitis	26	(4.9)	35	(6.6)	288	(14.2)	201	(2.6)
Neuropathy peripheral	21	(4.0)	29	(5.4)	221	(10.9)	146	(1.9)
Pneumonia	16	(3.0)	20	(3.7)	218	(10.7)	487	(6.4)
Neutropenia	1	(0.2)	0	(0.0)	663	(32.6)	82	(1.1)
Thrombocytopenia	0	(0.0)	0	(0.0)	401	(19.7)	117	(1.5)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for HBC (KN966: 15DEC2022)

Table 52 Participants With Drug-Related Adverse Events by Decreasing Incidence (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
with one or more adverse events	493	(93.2)	500	(93.6)	1,948	(95.8)	5,462	(71.6)
with no adverse events	36	(6.8)	34	(6.4)	85	(4.2)	2,169	(28.4)
Neutrophil count decreased	321	(60.7)	320	(59.9)	362	(17.8)	34	(0.4)
Anaemia	278	(52.6)	269	(50.4)	887	(43.6)	234	(3.1)
Platelet count decreased	199	(37.6)	197	(36.9)	240	(11.8)	43	(0.6)
Nausea	195	(36.9)	219	(41.0)	914	(45.0)	675	(8.8)
Fatigue	154	(29.1)	147	(27.5)	639	(31.4)	1,476	(19.3)
White blood cell count decreased	139	(26.3)	124	(23.2)	297	(14.6)	34	(0.4)
Decreased appetite	103	(19.5)	104	(19.5)	463	(22.8)	525	(6.9)
Vomiting	86	(16.3)	101	(18.9)	430	(21.2)	248	(3.2)
Constipation	85	(16.1)	74	(13.9)	272	(13.4)	184	(2.4)
Rash	73	(13.8)	37	(6.9)	267	(13.1)	884	(11.6)
Alanine aminotransferase increased	56	(10.6)	71	(13.3)	219	(10.8)	336	(4.4)
Pyrexia	55	(10.4)	35	(6.6)	137	(6.7)	314	(4.1)
Alopecia	53	(10.0)	65	(12.2)	430	(21.2)	57	(0.7)
Diarrhoea	53	(10.0)	55	(10.3)	431	(21.2)	904	(11.8)
Pruritus	52	(9.8)	31	(5.8)	202	(9.9)	1,143	(15.0)
Asthenia	51	(9.6)	81	(15.2)	273	(13.4)	491	(6.4)
Hypomagnesaemia	49	(9.3)	61	(11.4)	100	(4.9)	37	(0.5)
Aspartate aminotransferase increased	45	(8.5)	60	(11.2)	207	(10.2)	312	(4.1)
Hypothyroidism	41	(7.8)	11	(2.1)	220	(10.8)	810	(10.6)
Blood creatinine increased	39	(7.4)	39	(7.3)	174	(8.6)	105	(1.4)
Oedema peripheral	31	(5.9)	32	(6.0)	91	(4.5)	126	(1.7)
Malaise	30	(5.7)	27	(5.1)	98	(4.8)	55	(0.7)
Dysgeusia	29	(5.5)	27	(5.1)	158	(7.8)	79	(1.0)
Leukopenia	25	(4.7)	12	(2.2)	220	(10.8)	32	(0.4)
Mucosal inflammation	24	(4.5)	23	(4.3)	207	(10.2)	57	(0.7)
Peripheral sensory neuropathy	24	(4.5)	21	(3.9)	154	(7.6)	35	(0.5)
Lymphocyte count decreased	20	(3.8)	27	(5.1)	82	(4.0)	64	(0.8)
Stomatitis	19	(3.6)	27	(5.1)	256	(12.6)	103	(1.3)
Neuropathy peripheral	16	(3.0)	23	(4.3)	180	(8.9)	54	(0.7)
Weight decreased	16	(3.0)	24	(4.5)	134	(6.6)	148	(1.9)
Myalgia	15	(2.8)	12	(2.2)	107	(5.3)	312	(4.1)
Arthralgia	9	(1.7)	11	(2.1)	141	(6.9)	661	(8.7)
Neutropenia	1	(0.2)	0	(0.0)	641	(31.5)	49	(0.6)
Thrombocytopenia	0	(0.0)	0	(0.0)	376	(18.5)	56	(0.7)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Table 53 Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
with one or more adverse events	451	(85.3)	449	(84.1)	1,583	(77.9)	3,514	(46.0)
with no adverse events	78	(14.7)	85	(15.9)	450	(22.1)	4,117	(54.0)
Neutrophil count decreased	257	(48.6)	253	(47.4)	254	(12.5)	10	(0.1)
Anaemia	152	(28.7)	154	(28.8)	374	(18.4)	275	(3.6)
Platelet count decreased	94	(17.8)	107	(20.0)	71	(3.5)	10	(0.1)
White blood cell count decreased	61	(11.5)	47	(8.8)	136	(6.7)	5	(0.1)
Cholangitis	29	(5.5)	23	(4.3)	2	(0.1)	5	(0.1)
Fatigue	26	(4.9)	22	(4.1)	117	(5.8)	166	(2.2)
Pneumonia	9	(1.7)	10	(1.9)	138	(6.8)	270	(3.5)
Neutropenia	0	(0.0)	0	(0.0)	413	(20.3)	21	(0.3)
Thrombocytopenia	0	(0.0)	0	(0.0)	157	(7.7)	23	(0.3)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Table 54 Participants With Grade 3-5 Drug-Related Adverse Events by Decreasing Incidence (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
with one or more adverse events	377	(71.3)	370	(69.3)	1,285	(63.2)	1,208	(15.8)
with no adverse events	152	(28.7)	164	(30.7)	748	(36.8)	6,423	(84.2)
Neutrophil count decreased	247	(46.7)	246	(46.1)	242	(11.9)	6	(0.1)
Anaemia	123	(23.3)	131	(24.5)	307	(15.1)	33	(0.4)
Platelet count decreased	85	(16.1)	99	(18.5)	68	(3.3)	2	(0.0)
White blood cell count decreased	61	(11.5)	46	(8.6)	130	(6.4)	2	(0.0)
Neutropenia	0	(0.0)	0	(0.0)	403	(19.8)	13	(0.2)
Thrombocytopenia	0	(0.0)	0	(0.0)	143	(7.0)	11	(0.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006:

03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Serious adverse event/deaths/other significant events

Table 55 Participants With Adverse Events Resulting in Death by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups of KEYNOTE-966) (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
with one or more adverse events	31	(5.9)	49	(9.2)	139	(6.8)	346	(4.5)
with no adverse events	498	(94.1)	485	(90.8)	1,894	(93.2)	7,285	(95.5)
Pneumonia	4	(0.8)	0	(0.0)	15	(0.7)	40	(0.5)
Death	3	(0.6)	5	(0.9)	15	(0.7)	49	(0.6)
Sepsis	3	(0.6)	6	(1.1)	6	(0.3)	11	(0.1)
Biliary tract infection	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Euthanasia	2	(0.4)	1	(0.2)	0	(0.0)	1	(0.0)
Abdominal abscess	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal infection	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
COVID-19	1	(0.2)	4	(0.7)	1	(0.0)	0	(0.0)
Cardiac arrest	1	(0.2)	0	(0.0)	9	(0.4)	9	(0.1)
Cholangitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Fungal sepsis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal haemorrhage	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Lower respiratory tract infection	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Malignant neoplasm progression	1	(0.2)	0	(0.0)	0	(0.0)	4	(0.1)
Myocardial infarction	1	(0.2)	0	(0.0)	3	(0.1)	6	(0.1)
Pneumocystis jirovecii pneumonia	1	(0.2)	0	(0.0)	1	(0.0)	1	(0.0)
Pneumonia aspiration	1	(0.2)	0	(0.0)	5	(0.2)	8	(0.1)
Pneumonia viral	1	(0.2)	0	(0.0)	1	(0.0)	0	(0.0)
Pneumonitis	1	(0.2)	0	(0.0)	4	(0.2)	8	(0.1)
Pulmonary embolism	1	(0.2)	3	(0.6)	3	(0.1)	10	(0.1)
Septic shock	1	(0.2)	1	(0.2)	8	(0.4)	11	(0.1)
Shock haemorrhagic	1	(0.2)	0	(0.0)	1	(0.0)	0	(0.0)
Acute kidney injury	0	(0.0)	2	(0.4)	4	(0.2)	3	(0.0)
Acute myocardial infarction	0	(0.0)	1	(0.2)	2	(0.1)	1	(0.0)
Biliary sepsis	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
COVID-19 pneumonia	0	(0.0)	2	(0.4)	0	(0.0)	1	(0.0)
Cerebral haemorrhage	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.0)

Cerebral infarction	0	(0.0)	3	(0.6)	1	(0.0)	0	(0.0)
Cerebral venous sinus thrombosis	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Cholangitis infective	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Cholecystitis	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Diarrhoea	0	(0.0)	1	(0.2)	1	(0.0)	1	(0.0)
Hepatic infection	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Hepatorenal syndrome	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Ileus	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Liver abscess	0	(0.0)	2	(0.4)	0	(0.0)	0	(0.0)
Lung abscess	0	(0.0)	1	(0.2)	1	(0.0)	0	(0.0)
Oesophageal varices haemorrhage	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Pneumococcal sepsis	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Pneumonia acinetobacter	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Pneumonia bacterial	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Post procedural complication	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	1	(0.2)	5	(0.2)	17	(0.2)
Spontaneous bacterial peritonitis	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Upper gastrointestinal haemorrhage	0	(0.0)	2	(0.4)	1	(0.0)	1	(0.0)

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MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Deaths due to drug-related AEs were reported in 1.5% of the pembrolizumab plus chemotherapy group and 0.6% of the placebo plus chemotherapy group; no drug-related AEs resulting in death were reported in more than 1 participant. In KEYNOTE-966, a total of 8 participants died of a drug-related AE, as assessed by the investigator, in the pembrolizumab plus chemotherapy group. Of the 8 deaths in the pembrolizumab plus chemotherapy group considered by the investigator as related to the study intervention, 5 were considered related to chemotherapy (cholangitis, lower respiratory tract infection,

myocardial infarction, pneumonia viral, septic shock), 2 were considered related to pembrolizumab (abdominal abscess and malignant neoplasm progression), and 1 was related to both chemotherapy and pembrolizumab (pneumonitis) (data not shown).

Table 56 Participants With Serious Adverse Events by Decreasing Incidence (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
with one or more adverse events	276	(52.2)	263	(49.3)	962	(47.3)	2,742	(35.9)
with no adverse events	253	(47.8)	271	(50.7)	1,071	(52.7)	4,889	(64.1)
Cholangitis	31	(5.9)	24	(4.5)	2	(0.1)	5	(0.1)
Pyrexia	30	(5.7)	12	(2.2)	35	(1.7)	79	(1.0)
Pneumonia	8	(1.5)	8	(1.5)	137	(6.7)	272	(3.6)

Every participant is counted a single time for each applicable row and column.

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407-NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

The proportion of participants with 1 or more drug-related SAEs was generally similar in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group (22.9% vs 15.7%). The most frequently reported drug related SAEs (incidence ≥1%) were platelet count decreased, neutrophil count decreased, pyrexia, anemia, febrile neutropenia, and pneumonitis in the pembrolizumab plus chemotherapy group, and platelet count decreased and febrile neutropenia in the

placebo plus chemotherapy group. No meaningful differences in the frequency of specific drug related SAEs were observed between the treatment groups (data not shown).

The proportion of participants with drug-related SAEs in the pembrolizumab plus chemotherapy group (22.9%) was generally similar to the Pooled Combination Dataset (27.1%) and higher compared with the RSD (11.0%) (data not shown).

Adverse Events of Special Interest (AEOSI) are immune-mediated events and infusion-related reactions causally associated with pembrolizumab. When adjusted for exposure, the overall AEOSI rate was 3.32 events/100 person-months in the pembrolizumab plus chemotherapy group, 4.20 events/100 person-months in the Pooled Combination Dataset, and 4.55 events/100 person-months in the RSD.

For 14.9% of participants in the pembrolizumab plus chemotherapy group in KEYNOTE-966, the maximum grade of AEOSI was Grade 1 or 2; for 7.2% of participants, the maximum Grade was 3 to 5. There was 1 fatal AEOSI (pneumonitis) in the pembrolizumab plus chemotherapy group considered related to both chemotherapy (gemcitabine) and pembrolizumab by the investigator (data not shown).

The AEOSI outcome was reported as resolved or resolving for 37.6% and 18.8% of participants, respectively, in the pembrolizumab plus chemotherapy group of KEYNOTE-966 at the time of data cutoff.

The most frequently reported AEOSI categories in the pembrolizumab plus chemotherapy group were hypothyroidism (8.7%), pneumonitis (4.9%), and hyperthyroidism (3.6%). The proportion of participants with an event in the AEOSI category of hepatitis in the pembrolizumab plus chemotherapy group was (1.7%) compared with the Pooled Combination Dataset (1.2%) and the RSD (1.0%). There were no reported events of cholangitis sclerosing, autoimmune cholangitis, or immune-mediated cholangitis in the pembrolizumab plus chemotherapy group in KEYNOTE-966 (data not shown).

Table 57 Adverse Event Summary for AEOSI (APaT Population)

	KN966 Pembrolizumab + Chemotherapy[d]		KN966 Placebo + Chemotherapy[d]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[e]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	529		534		2,033		7,631	
with one or more adverse events	117	(22.1)	69	(12.9)	585	(28.8)	2,047	(26.8)
with no adverse event	412	(77.9)	465	(87.1)	1,448	(71.2)	5,584	(73.2)
with drug-related[a] adverse events	99	(18.7)	57	(10.7)	513	(25.2)	1,795	(23.5)
with toxicity grade 3-5 adverse events	38	(7.2)	21	(3.9)	168	(8.3)	527	(6.9)
with toxicity grade 3-5 drug-related adverse events	33	(6.2)	17	(3.2)	150	(7.4)	465	(6.1)
with serious adverse events	31	(5.9)	18	(3.4)	142	(7.0)	506	(6.6)
with serious drug-related adverse events	26	(4.9)	15	(2.8)	128	(6.3)	453	(5.9)
who died	1	(0.2)	0	(0.0)	6	(0.3)	13	(0.2)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)	6	(0.3)	13	(0.2)
discontinued any drug due to an adverse event	24	(4.5)	9	(1.7)	116	(5.7)	358	(4.7)
discontinued pembrolizumab or placebo	23	(4.3)	9	(1.7)	98	(4.8)	358	(4.7)
discontinued any chemotherapy	14	(2.6)	4	(0.7)	57	(2.8)	0	(0.0)
discontinued any drug due to a drug-related adverse event	24	(4.5)	9	(1.7)	113	(5.6)	352	(4.6)
discontinued pembrolizumab or placebo	23	(4.3)	9	(1.7)	95	(4.7)	352	(4.6)
discontinued any chemotherapy	14	(2.6)	4	(0.7)	55	(2.7)	0	(0.0)
discontinued any drug due to a serious adverse event	13	(2.5)	4	(0.7)	85	(4.2)	227	(3.0)
discontinued pembrolizumab or placebo	13	(2.5)	4	(0.7)	78	(3.8)	227	(3.0)
discontinued any chemotherapy	10	(1.9)	2	(0.4)	39	(1.9)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	13	(2.5)	4	(0.7)	82	(4.0)	225	(2.9)
discontinued pembrolizumab or placebo	13	(2.5)	4	(0.7)	75	(3.7)	225	(2.9)
discontinued any chemotherapy	10	(1.9)	2	(0.4)	37	(1.8)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03, with the exception of KN966 (version 5.0)

[d] Includes all participants who received at least one dose of pembrolizumab or chemotherapy in KN966.

[e] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158 cohort K, KN164 cohort A+B, KN177, KN204, KN564 and KN716.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407 and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN021 cohort A/C/G-NSCLC: 19AUG2019, KN024: 10JUL2017, KN042: 04SEP2018, KN189-NSCLC: 20MAY2019, KN407- NSCLC: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164 cohort A+B: 9SEP2019, KN177: 19FEB2021)

Database cutoff date for MSI-H (KN158 cohort K: 05OCT2020)

Database cutoff date for RCC (KN564-RCC: 14JUN2021)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for HBC (KN966: 15DEC2022)

Hepatic Events of Clinical Interest (HECI):

Patients with BTC are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. For careful monitoring of participants' hepatic events of clinical interest (HECI) criteria were defined in the protocol and used by the investigators for assessment and reporting of events meeting these criteria. In KEYNOTE-966, the median time to onset of the first HECI was 88.0 days (range 3 to 711 days) in the pembrolizumab plus chemotherapy group and 146.0 (range 2 to 579 days) in the placebo plus chemotherapy group.

With regard to pre-existing viral hepatitis, KEYNOTE-966 allowed enrollment of participants with preexisting HBV/HCV, and these participants were monitored during the course of the study. No cases of viral hepatitis flares were observed.

Table 58 Adverse Event Summary Hepatic Events of Clinical Interest (APaT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	529		534	
with one or more adverse events	49	(9.3)	57	(10.7)
with no adverse event	480	(90.7)	477	(89.3)
with drug-related[a] adverse events	17	(3.2)	14	(2.6)
with toxicity grade 3-5 adverse events	48	(9.1)	52	(9.7)
with toxicity grade 3-5 drug-related adverse events	16	(3.0)	13	(2.4)
with serious adverse events	36	(6.8)	39	(7.3)
with serious drug-related adverse events	8	(1.5)	7	(1.3)
who died	3	(0.6)	3	(0.6)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	15	(2.8)	9	(1.7)
discontinued MK-3475/PLACEBO	12	(2.3)	8	(1.5)
discontinued any chemotherapy	11	(2.1)	4	(0.7)
discontinued all drugs	6	(1.1)	1	(0.2)
discontinued any drug due to a drug-related adverse event	8	(1.5)	5	(0.9)
discontinued MK-3475/PLACEBO	7	(1.3)	4	(0.7)
discontinued any chemotherapy	5	(0.9)	1	(0.2)
discontinued all drugs	3	(0.6)	0	(0.0)
discontinued any drug due to a serious adverse event	11	(2.1)	6	(1.1)
discontinued MK-3475/PLACEBO	9	(1.7)	6	(1.1)
discontinued any chemotherapy	9	(1.7)	3	(0.6)
discontinued all drugs	5	(0.9)	1	(0.2)
discontinued any drug due to a serious drug-related adverse event	4	(0.8)	2	(0.4)
discontinued MK-3475/PLACEBO	4	(0.8)	2	(0.4)
discontinued any chemotherapy	3	(0.6)	0	(0.0)
discontinued all drugs	2	(0.4)	0	(0.0)

[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.

Table 59 Participants with Adverse Events Hepatic Events of Clinical Interest by Decreasing incidence (Incidence >0% in one or more treatment groups) (APaT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	529		534	
with one or more hepatic events of clinical interest	49	(9.3)	57	(10.7)
with no hepatic events of clinical interest	480	(90.7)	477	(89.3)
Biliary obstruction	7	(1.3)	9	(1.7)
Cholangitis	7	(1.3)	7	(1.3)
Ascites	6	(1.1)	2	(0.4)
Alanine aminotransferase increased	5	(0.9)	4	(0.7)
Biliary tract infection	5	(0.9)	5	(0.9)
Blood bilirubin increased	4	(0.8)	7	(1.3)
Immune-mediated hepatitis	4	(0.8)	6	(1.1)
Transaminases increased	3	(0.6)	2	(0.4)
Cholangitis acute	2	(0.4)	0	(0.0)
Jaundice cholestatic	2	(0.4)	4	(0.7)
Oesophageal varices haemorrhage	2	(0.4)	0	(0.0)
Sepsis	2	(0.4)	0	(0.0)
Autoimmune hepatitis	1	(0.2)	0	(0.0)
Biliary dilatation	1	(0.2)	1	(0.2)
Cholestasis	1	(0.2)	0	(0.0)
Cholestatic liver injury	1	(0.2)	0	(0.0)
Coombs negative haemolytic anaemia	1	(0.2)	0	(0.0)
Device dislocation	1	(0.2)	0	(0.0)
Hepatic encephalopathy	1	(0.2)	1	(0.2)
Hepatic function abnormal	1	(0.2)	0	(0.0)
Hepatic haemorrhage	1	(0.2)	0	(0.0)
Intestinal varices haemorrhage	1	(0.2)	0	(0.0)
Liver injury	1	(0.2)	0	(0.0)
Stent malfunction	1	(0.2)	0	(0.0)
Abdominal pain	0	(0.0)	1	(0.2)
Biliary sepsis	0	(0.0)	1	(0.2)
Cholangitis infective	0	(0.0)	2	(0.4)
Device occlusion	0	(0.0)	1	(0.2)
Drug-induced liver injury	0	(0.0)	1	(0.2)
Hyperbilirubinaemia	0	(0.0)	1	(0.2)
Hypertransaminasaemia	0	(0.0)	2	(0.4)
Jaundice	0	(0.0)	1	(0.2)
Liver abscess	0	(0.0)	2	(0.4)
Liver function test increased	0	(0.0)	1	(0.2)
Steatohepatitis	0	(0.0)	1	(0.2)
Upper gastrointestinal haemorrhage	0	(0.0)	1	(0.2)

Every participant is counted a single time for each applicable row and column.
MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 15DEC2022.

Figure 15 Between-Treatment comparisons in Hepatic Events of Clinical Interest Selected Adverse Events (>=1% incidence) and sorted by Risk Difference (APaT population)

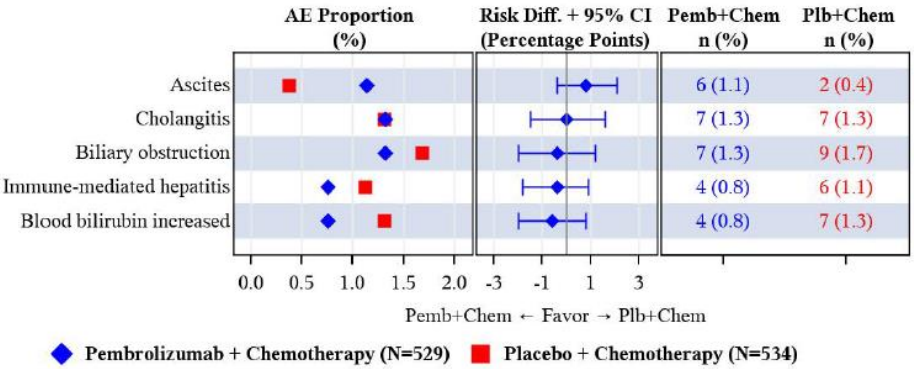

Table 60 Summary of Outcome for participants with hepatic events of clinical interest (Incidence >0% in one or more treatment groups (APaT population)

	Outcome	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy
		n (%)	n (%)
Participants in population		529	534
With one or more hepatic events of clinical interest	**Overall**	**49 (9.3)**	**57 (10.7)**
	Fatal	3 (6.1)	3 (5.3)
	Not Resolved	12 (24.5)	14 (24.6)
	Resolving	5 (10.2)	1 (1.8)
	Unknown	0 (0.0)	0 (0.0)
	Sequelae	0 (0.0)	1 (1.8)
	Resolved	29 (59.2)	38 (66.7)

Data were provided regarding the risk of Cholangitis and/or Biliary Infections including in patients with biliary stent/biliary drain:

Table 61 Adverse Event Summary Cholangitis and/or Biliary Infections (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	529		534	
with one or more adverse events	59	(11.2)	55	(10.3)
with no adverse event	470	(88.8)	479	(89.7)
with drug-related[a] adverse events	5	(0.9)	3	(0.6)
with toxicity grade 3-5 adverse events	52	(9.8)	48	(9.0)
with toxicity grade 3-5 drug-related adverse events	4	(0.8)	3	(0.6)
with serious adverse events	53	(10.0)	49	(9.2)
with serious drug-related adverse events	4	(0.8)	3	(0.6)
who died	3	(0.6)	2	(0.4)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)
discontinued any drug due to an adverse event	6	(1.1)	6	(1.1)
discontinued MK-3475/PLACEBO	4	(0.8)	6	(1.1)
discontinued any chemotherapy	5	(0.9)	5	(0.9)
discontinued all drugs	3	(0.6)	3	(0.6)
discontinued any drug due to a drug-related adverse event	1	(0.2)	2	(0.4)
discontinued MK-3475/PLACEBO	0	(0.0)	2	(0.4)

discontinued any chemotherapy	1	(0.2)	2	(0.4)
discontinued all drugs	0	(0.0)	1	(0.2)
discontinued any drug due to a serious adverse event	5	(0.9)	6	(1.1)
discontinued MK-3475/PLACEBO	4	(0.8)	6	(1.1)
discontinued any chemotherapy	4	(0.8)	5	(0.9)
discontinued all drugs	3	(0.6)	3	(0.6)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	2	(0.4)
discontinued MK-3475/PLACEBO	0	(0.0)	2	(0.4)
discontinued any chemotherapy	0	(0.0)	2	(0.4)
discontinued all drugs	0	(0.0)	1	(0.2)

[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.

Table 62 Summary of Outcome for Participants With Cholangitis Or Biliary Infections (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Outcome	Pembrolizumab + Chemotherapy n (%)	Placebo + Chemotherapy n (%)
Participants in population		529	534
With one or more cholangitis or biliary infections	**Overall**	**59 (11.2)**	**55 (10.3)**
	Fatal	3 (5.1)	2 (3.6)
	Not Resolved	8 (13.6)	7 (12.7)
	Resolving	2 (3.4)	3 (5.5)
	Unknown	0 (0.0)	0 (0.0)
	Sequelae	1 (1.7)	2 (3.6)
	Resolved	45 (76.3)	41 (74.5)

Every participant is counted once according to the worst outcome; the ordering of the outcome is as follows: Fatal>Not Resolved>Resolving>Unknown>Sequelae>Resolved.

"Participants in population" is used for percentage calculation for the Overall row in each section. Within each section, the overall total is used for percentage calculation for each outcome.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Database Cutoff Date: 15DEC2022.

Table 63 Adverse Event Summary Cholangitis and/or Biliary Infections (APaT Population – Biliary Stent/Biliary Drain)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	33		41	
with one or more adverse events	13	(39.4)	12	(29.3)
with no adverse event	20	(60.6)	29	(70.7)
with drug-related[a] adverse events	1	(3.0)	1	(2.4)
with toxicity grade 3-5 adverse events	13	(39.4)	10	(24.4)
with toxicity grade 3-5 drug-related adverse events	1	(3.0)	1	(2.4)
with serious adverse events	12	(36.4)	10	(24.4)

with serious drug-related adverse events	1	(3.0)	1	(2.4)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	2	(6.1)	1	(2.4)
discontinued MK-3475/PLACEBO	2	(6.1)	1	(2.4)
discontinued any chemotherapy	1	(3.0)	1	(2.4)
discontinued all drugs	1	(3.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	0	(0.0)	1	(2.4)
discontinued MK-3475/PLACEBO	0	(0.0)	1	(2.4)
discontinued any chemotherapy	0	(0.0)	1	(2.4)
discontinued all drugs	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	2	(6.1)	1	(2.4)
discontinued MK-3475/PLACEBO	2	(6.1)	1	(2.4)
discontinued any chemotherapy	1	(3.0)	1	(2.4)
discontinued all drugs	1	(3.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	1	(2.4)
discontinued MK-3475/PLACEBO	0	(0.0)	1	(2.4)
discontinued any chemotherapy	0	(0.0)	1	(2.4)
discontinued all drugs	0	(0.0)	0	(0.0)

[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.

Table 64 Summary of Outcome for Participants With Cholangitis Or Biliary Infections (Incidence > 0% in One or More Treatment Groups) (APaT Population - Biliary Stent/Biliary Drain)

	Outcome	Pembrolizumab + Chemotherapy n (%)	Placebo + Chemotherapy n (%)
Participants in population		33	41
With one or more cholangitis or biliary infections	**Overall**	**13 (39.4)**	**12 (29.3)**
	Fatal	0 (0.0)	0 (0.0)
	Not Resolved	2 (15.4)	1 (8.3)
	Resolving	0 (0.0)	2 (16.7)
	Unknown	0 (0.0)	0 (0.0)
	Sequelae	0 (0.0)	1 (8.3)
	Resolved	11 (84.6)	8 (66.7)

Every participant is counted once according to the worst outcome; the ordering of the outcome is as follows: Fatal>Not Resolved>Resolving>Unknown>Sequelae>Resolved.

"Participants in population" is used for percentage calculation for the Overall row in each section. Within each section, the overall total is used for percentage calculation for each outcome.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Database Cutoff Date: 15DEC2022.

Laboratory findings

No new safety concerns based on laboratory abnormalities were reported in the pembrolizumab plus chemotherapy group in KEYNOTE-966. The proportion of participants with abnormal laboratory findings were comparable in the pembrolizumab plus chemotherapy and placebo plus chemotherapy group, and higher than the RSD, reflecting chemotherapy-related toxicities and the study indication. There were no notable differences in laboratory abnormalities between the treatment groups in KEYNOTE-966 (tables not shown). Laboratory abnormalities (by maximum toxicity grade worsened from baseline) in the KEYNOTE-966 pembrolizumab plus chemotherapy group versus the RSD (≥20% difference) included ALT increased, AST increased, bilirubin increased, calcium decreased, creatinine increased, GGT increased, sodium decreased, hypomagnesemia, white blood cell count decreased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, hemoglobin decreased (anemia). The laboratory abnormalities listed above were primarily CTCAE Grade 1 and Grade 2 in severity. The most frequently observed (≥10%) Grade 3 or 4 laboratory abnormalities that were similar in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups were consistent with chemotherapy-related myelosuppression (WBC decreased, hemoglobin decreased, platelet count decreased, lymphocyte count decreased, neutrophil count decreased), or underlying advanced BTC (blood bilirubin increased) (tables not shown).

Safety in special populations

Age

Table 65 Adverse Event Summary by Age Category (<65, 65-74, >=75 years) (APaT population)

	KN966 Pembrolizumab + Chemotherapy[d]						KN966 Placebo + Chemotherapy[d]						Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]					
	<65		65-74		>=75		<65		65-74		>=75		<65		65-74		>=75	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	266		195		68		296		181		57		1,218		653		162	
with one or more adverse events	261	(98.1)	195	(100.0)	68	(100.0)	296	(100.0)	179	(98.9)	57	(100.0)	1,207	(99.1)	647	(99.1)	161	(99.4)
with no adverse event	5	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	11	(0.9)	6	(0.9)	1	(0.6)
with drug-related[a] adverse events	244	(91.7)	186	(95.4)	63	(92.6)	281	(94.9)	172	(95.0)	47	(82.5)	1,165	(95.6)	629	(96.3)	154	(95.1)
with toxicity grade 3-5 adverse events	224	(84.2)	168	(86.2)	59	(86.8)	241	(81.4)	158	(87.3)	50	(87.7)	940	(77.2)	506	(77.5)	137	(84.6)
with toxicity grade 3-5 drug-related adverse events	179	(67.3)	150	(76.9)	48	(70.6)	193	(65.2)	138	(76.2)	39	(68.4)	760	(62.4)	422	(64.6)	103	(63.6)
with serious adverse events	128	(48.1)	103	(52.8)	45	(66.2)	133	(44.9)	93	(51.4)	37	(64.9)	512	(42.0)	353	(54.1)	97	(59.9)
with serious drug-related adverse events	61	(22.9)	38	(19.5)	22	(32.4)	34	(11.5)	39	(21.5)	11	(19.3)	289	(23.7)	205	(31.4)	56	(34.6)
with any dose modification[b] due to an adverse event	211	(79.3)	166	(85.1)	57	(83.8)	233	(78.7)	158	(87.3)	50	(87.7)	910	(74.7)	534	(81.8)	137	(84.6)
pembrolizumab or placebo dose modification	153	(57.5)	128	(65.6)	47	(69.1)	177	(59.8)	118	(65.2)	44	(77.2)	706	(58.0)	447	(68.5)	117	(72.2)
any chemotherapy dose modification	56	(21.1)	45	(23.1)	23	(33.8)	45	(15.2)	42	(23.2)	26	(45.6)	--		--		--	
who died	11	(4.1)	10	(5.1)	10	(14.7)	22	(7.4)	15	(8.3)	12	(21.1)	58	(4.8)	49	(7.5)	32	(19.8)
who died due to a drug-related adverse event	4	(1.5)	2	(1.0)	2	(2.9)	0	(0.0)	2	(1.1)	1	(1.8)	17	(1.4)	15	(2.3)	11	(6.8)
discontinued any drug due to an adverse event	62	(23.3)	51	(26.2)	25	(36.8)	52	(17.6)	44	(24.3)	26	(45.6)	275	(22.6)	209	(32.0)	67	(41.4)
discontinued pembrolizumab or placebo	33	(12.4)	28	(14.4)	16	(23.5)	29	(9.8)	21	(11.6)	16	(28.1)	162	(13.3)	131	(20.1)	52	(32.1)
discontinued any chemotherapy	56	(21.1)	45	(23.1)	23	(33.8)	45	(15.2)	42	(23.2)	26	(45.6)	--		--		--	
discontinued any drug due to a drug-related adverse event	48	(18.0)	37	(19.0)	17	(25.0)	36	(12.2)	31	(17.1)	14	(24.6)	228	(18.7)	161	(24.7)	45	(27.8)
discontinued pembrolizumab or placebo	20	(7.5)	19	(9.7)	8	(11.8)	16	(5.4)	7	(3.9)	3	(5.3)	116	(9.5)	88	(13.5)	30	(18.5)
discontinued any chemotherapy	43	(16.2)	32	(16.4)	15	(22.1)	30	(10.1)	29	(16.0)	14	(24.6)	--		--		--	
discontinued any drug due to a serious adverse event	35	(13.2)	23	(11.8)	18	(26.5)	22	(7.4)	22	(12.2)	17	(29.8)	154	(12.6)	122	(18.7)	51	(31.5)
discontinued pembrolizumab or placebo	29	(10.9)	17	(8.7)	15	(22.1)	20	(6.8)	19	(10.5)	15	(26.3)	120	(9.9)	101	(15.5)	47	(29.0)
discontinued any chemotherapy	30	(11.3)	21	(10.8)	16	(23.5)	19	(6.4)	17	(9.4)	16	(28.1)	--		--		--	
discontinued any drug due to a serious drug-related adverse event	23	(8.6)	9	(4.6)	9	(13.2)	8	(2.7)	8	(4.4)	4	(7.0)	112	(9.2)	78	(11.9)	30	(18.5)
discontinued pembrolizumab or placebo	17	(6.4)	8	(4.1)	7	(10.3)	7	(2.4)	5	(2.8)	2	(3.5)	79	(6.5)	62	(9.5)	26	(16.0)

Sex. The AE profile in the pembrolizumab plus chemotherapy group in KEYNOTE-966 was generally similar between male and female participants (tables not shown). The AE profile was similar for both sexes in the Pooled Combination Dataset (with the exception of SAEs, which were more common in males) and the RSD (data not shown).

ECOG Status. The AE profile in the pembrolizumab plus chemotherapy group in KEYNOTE-966 was generally similar between participants with an ECOG status of 0 and participants with an ECOG status of 1, except for a higher incidence of all causality SAEs in participants with an ECOG status of 1 (data not shown).

The same pattern (higher incidence of all causality SAEs in participants with an ECOG status of 1 vs 0) was generally observed in the Pooled Combination Dataset and the RSD. Additionally, the incidence of drug-related SAEs was higher in participants with ECOG status of 1 vs 0 in the Pooled Combination Dataset, the incidence of Grade 3 to 5 all causality AEs was higher in participants with ECOG status of 1 vs 0 in the RSD, and the incidence of drug-related AEs was higher in participants with ECOG status of 0 vs 1 in the RSD.

Region. The AE profile based on region in the pembrolizumab plus chemotherapy group in KEYNOTE-966 was generally consistent with both the Pooled Combination Dataset and the RSD. No notable differences in AE profile were observed between North America, Western Europe, and the rest of the world (data not shown).

Use in Pregnancy and Lactation. There were no reports of pregnancy in KEYNOTE-966.

Safety related to drug-drug interactions and other interactions

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and drug-drug interaction (DDI) are not anticipated to influence exposure.

Drugs that affect the cytochrome P450 enzymes, and other metabolizing enzymes, are not expected to interfere with the metabolism of an IgG antibody. The IgG antibodies, in general, do not directly regulate the expression of cytochrome P450 enzymes, other enzymes, or transporters involved in drug elimination. Therefore, no dedicated DDI studies have been performed. In addition, *in vitro* experiments and studies conducted in preclinical species have been shown to have limited value in predicting DDI potential in humans. Therefore, no preclinical pharmacokinetic studies were conducted to assess the propensity of pembrolizumab to be a victim or perpetrator of pharmacokinetic DDIs. Similarly, the potential of DDI between pembrolizumab and chemotherapy agents is expected to be low. No impact of co-administered chemotherapy on pembrolizumab PK was observed in KEYNOTE-021 cohort G. Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. However, as systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was assessed as part of the population pharmacokinetic analysis (data not shown). No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Nevertheless, the use of systemic corticosteroids or other immunosuppressants before the start of pembrolizumab treatment should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab treatment to treat immune-mediated adverse reactions. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions (see section 4.5 of the SmPC).

Discontinuation due to adverse events

In KEYNOTE-966, the proportion of participants in the pembrolizumab plus chemotherapy group who experienced 1 or more AEs that led to discontinuation of any study treatment was generally similar compared with the placebo plus chemotherapy group (26.1% vs 22.8% (see Table 49), exposure adjusted 3.43 vs 3.18 (see Table 50)). The incidence of specific AEs was similar between both treatment

groups in KEYNOTE-966 (see Table 51). The proportion of participants discontinuing any study treatment due to cholangitis was low in both the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups (0.4% and 0.6%, respectively) (data not shown).

The proportion of participants with AEs leading to discontinuations of any study treatment in the pembrolizumab plus chemotherapy group (26.1%) was similar to the Pooled Combination Dataset (27.1%) and higher compared with the RSD (14.0%) (see Table 49); differences between the pembrolizumab plus chemotherapy group and the RSD were driven partly by chemotherapy-related toxicities (neutrophil count decreased and platelet count decreased) (data not shown).

A similar percentage of participants in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups in KEYNOTE-966 experienced AEs leading to discontinuation of chemotherapy (23.4% and 21.2%, respectively). These percentages were also similar to the percentage of participants with AEs leading to discontinuation of chemotherapy in the Pooled Combination Dataset (20.9%) (see Table 49).

Discontinuation of pembrolizumab/placebo due to AEs occurred in a similar proportion of participants in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups (14.6% vs 12.4%). These percentages were also generally consistent with the Pooled Combination Dataset (17.0%) and the RSD (14.0%), with no clinically meaningful differences in AEs between the groups and indicate no new safety concern for pembrolizumab (see Table 49).

In KEYNOTE-966, the proportion of participants with drug-related AEs leading to discontinuation of any study treatment was generally similar in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group (19.3% vs 15.2%) (see Table 49). The most frequently reported AEs (≥1% incidence) leading to discontinuation of any study treatment in both treatment groups were neutrophil count decreased, and blood creatinine increased (data not shown).

The proportion of participants with drug-related AEs leading to discontinuation of any study treatment in the pembrolizumab plus chemotherapy group (19.3%) was similar to the Pooled Combination Dataset (21.3%) and higher compared with the RSD (8.4%) (see Table 49). Differences in the pembrolizumab plus chemotherapy group compared with the RSD were partly driven by higher incidences of chemotherapy-associated AEs (e.g., neutrophil count decreased, platelet count decreased) (data not shown).

In KEYNOTE-966, the proportion of participants with drug-related AEs leading to discontinuation of pembrolizumab/placebo was generally similar in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups (8.9% vs 4.9%) (see Table 49). The most frequently reported drug-related AEs (≥2 participants) leading to discontinuation of pembrolizumab in the pembrolizumab plus chemotherapy group were pneumonitis, platelet count decreased, enterocolitis, pulmonary embolism, immune-mediated hepatitis, and autoimmune hepatitis (data not shown).

The proportion of participants in the pembrolizumab plus chemotherapy group with drug-related AEs leading to discontinuation of pembrolizumab (8.9%) was similar to those in the both the Pooled Combination Dataset (11.5%) and the RSD (8.4%) (see Table 49).

Participant narratives for participants in pembrolizumab plus chemotherapy group with drug-related AEs leading to discontinuation of intervention are provided in the CSR (data not shown). The proportion of participants who experienced 1 or more AEs that led to interruption of any study treatment was similar in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group (70.5% vs 70.6%). The most frequently reported AEs (≥5%) in both groups were neutrophil count decreased, platelet count decreased, WBC count decreased, and anemia, reflecting common chemotherapy-related toxicities (data not shown).

The proportion of participants with AEs leading to interruption of any study treatment in the pembrolizumab plus chemotherapy group (70.5%) was similar to the Pooled Combination Dataset (64.5%) and higher compared with the RSD (26.1%) (data not shown).

The proportion of participants with AEs resulting in treatment interruptions of pembrolizumab/placebo was similar in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups (55.0% vs 58.1%). The most frequently reported AEs (≥5% incidence) leading to pembrolizumab/placebo interruptions included neutrophil count decreased, platelet count decreased, and anemia, consistent with common chemotherapy-related toxicities (data not shown).

The proportion of participants with treatment interruptions of pembrolizumab due to AEs in the pembrolizumab plus chemotherapy group (55.0%) was similar to the Pooled Combination Dataset (54.9%) and higher compared with the RSD (26.1%). Differences between the pembrolizumab plus chemotherapy group and the RSD were partly driven by higher incidences of chemotherapy-associated AEs (neutrophil count decreased, platelet count decreased, and anemia) (data not shown).

The proportion of participants with drug-related AEs leading to interruption of any study treatment was similar in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group (56.9% vs 57.1%). The most frequently reported drug-related AEs (≥5%) in both groups were neutrophil count decreased, platelet count decreased, WBC count decreased, and anemia, reflecting common chemotherapy-related toxicities. The proportion of participants with drug-related AEs leading to interruption of any study treatment in the pembrolizumab plus chemotherapy group was also similar to that observed in the Pooled Combination Dataset (54.5%) (data not shown).

The proportion of participants with treatment interruption due to drug-related AEs was higher in the pembrolizumab plus chemotherapy group compared with the RSD (56.9% vs 14.7%). Differences were partly driven by higher incidences of chemotherapy-associated AEs (neutrophil count decreased, platelet count decreased, WBC count decreased, and anemia) (data not shown).

The proportion of participants with treatment interruptions of pembrolizumab/placebo were similar in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups (38.6% vs 40.6%). The most frequently reported drug-related AEs (≥5% incidence) in these groups included neutrophil count decreased, platelet count decreased, and anemia, consistent with common chemotherapy-related toxicities (data not shown).

The proportion of participants with treatment interruptions of pembrolizumab due to drug-related AEs was higher in the pembrolizumab plus chemotherapy group compared with the RSD (38.6% vs 14.7%) (data not shown).

Adverse drug reactions (ADRs)

Section 4.8 of the SmPC has been updated to reflect the addition of the KEYNOTE-966 population of BTC patients, receiving pembrolizumab in combination with gemcitabine and cisplatin, into the current ‘pembrolizumab in combination with chemotherapy’ pooled dataset (N=4787).

Table 66 Adverse reactions in patients treated with pembrolizumab in combination with chemotherapy

		Combination Therapy (N=4787)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	7.3% (349)	196
Blood and lymphatic system disorders			
Very common	Anaemia	52.5% (2513)	911
Very common	Neutropenia	27.5% (1318)	808
Very common	Thrombocytopenia	14.8% (708)	227
Common	Febrile Neutropenia	5.9% (284)	274
Common	Leukopenia	9.4% (452)	163
Common	Lymphopenia	3.0% (145)	44
Uncommon	Eosinophilia	0.6% (28)	2
Rare	Haemolytic Anaemia	0.06% (3)	2
Rare	Immune Thrombocytopenia	0.06% (3)	2
Immune system disorders			
Common	Infusion Reactionsa	7.4% (354)	64
Rare	Sarcoidosis	0.02% (1)	0
Endocrine disorders			
Very common	Hypothyroidismb	13.3% (637)	16
Common	Adrenal Insufficiencyc	1.2% (57)	24
Common	Thyroiditisd	1.2% (57)	6
Common	Hyperthyroidism	5.2% (248)	5
Uncommon	Hypophysitise	0.8% (37)	19
Rare	Hypoparathyroidism	0.04% (2)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	11.6% (554)	176
Very common	Decreased Appetite	27.9% (1335)	107
Common	Hyponatraemia	7.7% (369)	165
Common	Hypocalcaemia	4.4% (210)	32
Uncommon	Type 1 Diabetes Mellitusf	0.4% (17)	16

		Combination Therapy (N=4787)	
		All AEs % (n)	Gr 3-5 AEs n
Psychiatric disorders			
Very common	Insomnia	10.5% (505)	6
Nervous system disorders			
Very common	Neuropathy Peripheral	14.8% (708)	51
Very common	Headache	14.0% (672)	15
Common	Dizziness	9.8% (467)	14
Common	Dysgeusia	8.9% (424)	2
Common	Lethargy	1.2% (56)	2
Uncommon	Encephalitisg	0.1% (7)	7
Uncommon	Epilepsy	0.1% (7)	3
Rare	Myasthenic Syndrome	0.06% (3)	3
Rare	Guillain-Barre Syndromeh	0.04% (2)	2
Rare	Optic Neuritis	0.02% (1)	1
Eye disorders			
Common	Dry Eye	3.1% (149)	1
Uncommon	Uveitisi	0.1% (5)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)j	3.6% (173)	45
Uncommon	Myocarditisk	0.2% (9)	7
Uncommon	Pericardial Effusion	0.4% (19)	7
Uncommon	Pericarditis	0.1% (7)	2
Vascular disorders			
Common	Hypertension	6.2% (295)	126
Uncommon	Vasculitisl	0.6% (31)	4
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	11.2% (535)	60
Very common	Cough	15.9% (762)	5

		Combination Therapy (N=4787)	
		All AEs % (n)	Gr 3-5 AEs n
Common	Pneumonitism	4.1% (196)	72
Gastrointestinal disorders			
Very common	Diarrhoea	34.2% (1637)	197
Very common	Vomiting	28.9% (1384)	173
Very common	Nausea	51.4% (2460)	163
Very common	Abdominal Painn	19.4% (929)	66
Very common	Constipation	31.8% (1522)	17
Common	Colitiso	2.8% (136)	68
Common	Gastritis	2.1% (100)	8
Common	Dry Mouth	4.6% (218)	1
Uncommon	Pancreatitisp	0.5% (22)	17
Uncommon	Gastrointestinal Ulcerationq	0.5% (22)	3
Rare	Small Intestinal Perforation	0.04% (2)	2
Hepatobiliary disorders			
Common	Hepatitisr	1.3% (60)	45
Rare	Cholangitis Sclerosings	0.04% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Alopecia	24.7% (1181)	6
Very common	Pruritust	14.3% (683)	5
Very common	Rashu	21.3% (1018)	4
Common	Severe Skin Reactionsv	2.6% (125)	109
Common	Erythema	3.8% (184)	3
Common	Dermatitis	1.5% (73)	3
Common	Dry Skin	5.3% (256)	2
Common	Dermatitis Acneiform	2.0% (97)	2
Common	Eczema	1.2% (58)	1
Uncommon	Psoriasis	0.4% (21)	4
Uncommon	Lichenoid Keratosisw	0.1% (5)	1
Uncommon	Vitiligox	0.6% (28)	0
Uncommon	Papule	0.2% (10)	0
Rare	Stevens-Johnson Syndrome	0.04% (2)	2

		Combination Therapy (N=4787)	
		All AEs % (n)	Gr 3-5 AEs n
Rare	Erythema Nodosum	0.08% (4)	0
Rare	Hair Colour Changes	0.02% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Painy	14.1% (677)	35
Very common	Arthralgia	15.8% (756)	31
Common	Myositisz	9.0% (432)	17
Common	Pain In Extremity	7.1% (342)	9
Common	Arthritisaa	1.6% (76)	7
Uncommon	Tenosynovitisbb	0.4% (18)	1
Rare	Sjogren's Syndrome	0.02% (1)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.5% (166)	83
Uncommon	Nephritiscc	0.7% (35)	19
Uncommon	Cystitis Noninfective	0.2% (8)	0
General disorders and administration site conditions			
Very common	Fatigue	34.7% (1662)	239
Very common	Asthenia	19.1% (912)	155
Very common	Pyrexia	19.0% (911)	40
Common	Oedemadd	4.6% (222)	8
Common	Influenza Like Illness	2.8% (133)	2
Common	Chills	2.9% (140)	0
Investigations			
Very common	Alanine Aminotransferase Increased	17.7% (846)	154
Very common	Aspartate Aminotransferase Increased	17.7% (847)	125
Common	Blood Bilirubin Increased	5.6% (270)	49
Common	Blood Alkaline Phosphatase Increased	6.6% (318)	39
Common	Blood Creatinine Increased	9.1% (435)	24
Common	Hypercalcaemia	1.7% (79)	20

		Combination Therapy (N=4787)	
		All AEs % (n)	Gr 3-5 AEs n
Uncommon	Amylase Increased	0.6% (28)	9

Every participant is counted a single time for each applicable row.

a. Infusion Reactions (Anaphylactic Reaction, Cytokine Release Syndrome, Drug Hypersensitivity, Hypersensitivity, Infusion Related Hypersensitivity Reaction, Infusion Related Reaction, Serum Sickness)

b. Hypothyroidism (Hypothyroidism, Immune-Mediated Hypothyroidism)

c. Adrenal Insufficiency (Addison's Disease, Adrenal Insufficiency)

d. Thyroiditis (Autoimmune Thyroiditis, Silent Thyroiditis, Thyroid Disorder, Thyroiditis, Thyroiditis Acute)

e. Hypophysitis (Hypophysitis, Hypopituitarism)

f. Type 1 Diabetes Mellitus (Diabetic Ketoacidosis, Type 1 Diabetes Mellitus)

g. Encephalitis (Encephalitis, Encephalitis Autoimmune)

h. Guillain-Barre Syndrome (Demyelinating Polyneuropathy, Guillain-Barre Syndrome)

i. Uveitis (Iridocyclitis, Uveitis)

j. Cardiac Arrhythmia (Including Atrial Fibrillation) (Arrhythmia, Atrial Fibrillation, Atrial Flutter, Atrial Tachycardia, Atrioventricular Block, Atrioventricular Block First Degree, Atrioventricular Block Second Degree, Bundle Branch Block, Cardiac Flutter, Electrocardiogram Qt Prolonged, Electrocardiogram Repolarisation Abnormality, Extrasystoles, Heart Rate Irregular, Sinus Arrhythmia, Sinus Bradycardia, Sinus Node Dysfunction, Sinus Tachycardia, Supraventricular Extrasystoles, Supraventricular Tachycardia, Ventricular Arrhythmia, Ventricular Extrasystoles, Ventricular Tachycardia)

k. Myocarditis (Autoimmune Myocarditis, Myocarditis)

l. Vasculitis (Central Nervous System Vasculitis, Vasculitis)

m. Pneumonitis (Autoimmune Lung Disease, Immune-Mediated Lung Disease, Interstitial Lung Disease, Organising Pneumonia, Pneumonitis)

n. Abdominal Pain (Abdominal Discomfort, Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper)

o. Colitis (Autoimmune Colitis, Colitis, Colitis Microscopic, Enterocolitis, Immune-Mediated Enterocolitis)

p. Pancreatitis (Pancreatitis, Pancreatitis Acute)

q. Gastrointestinal Ulceration (Duodenal Ulcer, Gastric Ulcer)

r. Hepatitis (Autoimmune Hepatitis, Hepatitis, Immune-Mediated Hepatitis)

s. Cholangitis Sclerosing (Cholangitis Sclerosing, Immune-Mediated Cholangitis)

t. Pruritus (Pruritus, Urticaria)

u. Rash (Genital Rash, Rash, Rash Erythematous, Rash Macular, Rash Maculo-Papular, Rash Papular, Rash Pruritic, Rash Vesicular)

v. Severe Skin Reactions (Cutaneous Vasculitis, Dermatitis Bullous, Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Erythema Multiforme, Pemphigoid, Pruritus, Rash, Rash Erythematous, Rash Maculo-Papular, Rash Pruritic, Rash Pustular, Stevens-Johnson Syndrome, Toxic Skin Eruption)

w. Lichenoid Keratosis (Lichen Planus, Lichenoid Keratosis)

x. Vitiligo (Skin Depigmentation, Skin Hypopigmentation, Vitiligo)

y. Musculoskeletal Pain (Back Pain, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal Pain, Musculoskeletal Stiffness)

z. Myositis (Myalgia, Myopathy, Myositis, Polymyalgia Rheumatica, Rhabdomyolysis)

aa. Arthritis (Arthritis, Immune-Mediated Arthritis, Joint Effusion, Joint Swelling, Polyarthritis)

bb. Tenosynovitis (Synovitis, Tendon Pain, Tendonitis, Tenosynovitis)

cc. Nephritis (Autoimmune Nephritis, Immune-Mediated Nephritis, Nephritis, Tubulointerstitial Nephritis)

dd. Oedema (Eyelid Oedema, Face Oedema, Fluid Retention, Generalised Oedema, Lip Oedema, Localised Oedema, Oedema, Periorbital Oedema)

Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407, KN522, KN590, KN811, KN826, KN859 and KN966.

Database cutoff date for BTC (KN966: 15DEC2022)

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2021 through 03-SEP-2022, specifically Appendix 20.3 (Numbers of Adverse Drug

Reactions by Preferred Term from Postauthorization Sources). No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

The safety profile of pembrolizumab in combination with cisplatin and gemcitabine in adult patients with locally advanced unresectable or metastatic biliary tract cancers has been assessed in the phase 3 randomized, placebo-controlled KEYNOTE-966 clinical trial. The safety analysis was presented as comparative of chemotherapy vs chemotherapy plus immunotherapy in the context of KEYNOTE-966. At data cut-off of 15-DEC-2022 (final analysis (FA)), all participants who received at least 1 dose of study intervention were included in the safety analysis (n=529 in the interventional arm; n=534 in the control arm). Additionally, the MAH provided safety data from the reference datasets of previous studies with pembrolizumab used as a single agent (n=7 631) or in combination with chemotherapy (n=2 033).

The KEYNOTE-966 **trial population** resulted enriched in subjects of Asian race (45.9% in the pembrolizumab plus chemotherapy group and 46.6% in the placebo plus chemotherapy group) as compared with the reference datasets of chemotherapy plus immunotherapy and immunotherapy alone (10.8 and23.2%, respectively). Such a difference is in part justified by the study indication, given the epidemiology of cholangiocarcinoma. The population was well balanced according to age, ECOG performance status and gender.

Exposure to the study drugs was similar in the pembrolizumab plus chemotherapy and chemotherapy plus placebo arms (median 6.37 vs 5.54 months), as it was for the mean number of administrations (20.35 vs 18.89 administrations). The slightly longer exposure in the pembrolizumab arm is likely a result of the longer progression-free survival.

The proportion of **AEs** reported in the two arms was comparable. However, treatment-related serious AEs were higher in subjects receiving pembrolizumab plus chemotherapy than chemotherapy alone (22.9% vs 15.7%). In addition, pruritus, rash and pyrexia were more common in patients receiving pembrolizumab; however, the incidence of these AEs was not higher than observed in the pooled datasets of pembrolizumab alone or in combination with various chemotherapies. Rash and pruritus have been associated with pembrolizumab. The differences in the safety profile between chemotherapy plus pembrolizumab and pembrolizumab alone were commonly ascribed to the chemo-related haematological toxicity, such as neutrophil count decreased, anaemia, platelet count decreased, nausea, white blood cell count (WBC) decreased, vomiting, constipation.

A higher proportion of participants in the pembrolizumab plus chemotherapy group experienced AEs of ALT increased and AST increased compared with the RSD, that could be associated with the study indication BTC. However, the frequency of ALT and AST increased was higher in the control arm of KEYNOTE-966 study.

A higher proportion of participants in the pembrolizumab plus chemotherapy group had **Grade 3 to 4 AEs** compared with the RSD, possibly due to chemotherapy and underlying malignancy in the KEYNOTE-966.

Overall, the proportion of participants in KEYNOTE-966 who experienced 1 or more **drug-related AEs** was similar between the pembrolizumab plus chemotherapy and the placebo plus chemotherapy groups (93.2% vs 93.6%). The most frequently reported drug-related AEs (incidence ≥10%) were similar between the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups. Consistently with the analysis of all AEs, pruritus, rash and hypothyroidism were more common in patients treated with pembrolizumab than placebo. The proportion of participants with drug-related AEs in the pembrolizumab plus chemotherapy group (93.2%) was similar to the Pooled Combination Dataset

(95.8%) and higher than in the RSD (71.6%). Common drug-related AEs in the pembrolizumab plus chemotherapy group included common chemotherapy-related toxicities of neutrophil count decreased, anemia, platelet count decreased, nausea, WBC decreased, fatigue, decreased appetite, vomiting, constipation, and rash.

Grade 3 to 5 adverse events occurred in a comparable proportion in the two study arms (85.3% vs 84.1%). The most frequently reported Grade 3 to 5 AEs (incidence ≥5%) in the pembrolizumab plus chemotherapy group were neutrophil count decreased, anaemia, platelet count decreased, WBC count decreased, and cholangitis. The proportion of participants with 1 or more drug-related SAEs was higher in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group (22.9% vs 15.7%). The most frequently reported drug-related SAEs (incidence ≥1%) were platelet count decreased, neutrophil count decreased, pyrexia, anaemia, febrile neutropenia, and pneumonitis in the pembrolizumab plus chemotherapy group, and platelet count decreased and febrile neutropenia in the placebo plus chemotherapy group. No meaningful differences in the frequency of specific drug-related SAEs were observed between the treatment groups. Also, when compared with the reference pooled dataset of pembrolizumab, with or without chemotherapy, cholangitis emerged as a more common event in KEYNOTE-966; however, such a difference can still be interpreted based on the study indication, that is biliary cancers.

Fatal events occurred in 5.9% and 9.2% of subjects enrolled in the pembrolizumab and placebo arm, respectively. The most frequently reported AEs resulting in death (>2 participants) in KEYNOTE-966 were pneumonia (0.8%), death (0.6%), and sepsis (0.6%) in the pembrolizumab plus chemotherapy group, and sepsis (1.1%), death (0.9%), COVID-19 (0.7%), cerebral infarction (0.6%), and pulmonary embolism (0.6%) in the placebo plus chemotherapy group. Deaths due to drug-related AEs were reported in 1.5% of the pembrolizumab plus chemotherapy group and 0.6% of the placebo plus chemotherapy group.

Clarifications were requested to the MAH on the event reported as "death" in the control arm, as it was unclear if this was a case of thyroiditis in a patient with pre-existing risk of fatal arrythmia, not managed in the proper way. The additional data provided however did not allow to conclude on a reasonable possibility of a causality between pembrolizumab and the event of death given the underlying cardiovascular and pulmonary comorbidities, reported sudden onset of the event, and a lack of an autopsy report.

Additional clarification regarding the event of death due to "viral pneumonia", based on the available data including fever, neutropenia, lymphopenia and CT imaging finding, it was agreed with the MAH that likely the event was secondary to an infectious process in the setting of underlying malignancy and administration of chemotherapy.

No new indication-specific **AEOSI** causally associated with pembrolizumab were identified in the pembrolizumab plus chemotherapy group in KEYNOTE-966.The frequency, severity, and types of AEOSI observed in the pembrolizumab plus chemotherapy group were generally consistent with pembrolizumab used as a single agent. The overall incidence of AEOSI was similar in the pembrolizumab plus chemotherapy group (22.1%) compared with Pooled Combination Dataset (28.8%) and the RSD (26.8%), and higher than chemotherapy alone (12.9%). There was 1 fatal AEOSI (pneumonitis) in the pembrolizumab plus chemotherapy group considered related to both chemotherapy (gemcitabine) and pembrolizumab by the investigator. Pneumonitis is a well-known adverse drug reaction of pembrolizumab, and the risk of fatal events of pneumonitis is already included in the SmPC. The proportion of participants with an event in the AEOSI category of hepatitis was similar in the pembrolizumab plus chemotherapy group (1.7%) compared with the Pooled Combination Dataset (1.2%) and the RSD (1.0%). Overall, there were no data suggesting any new safety concerns for known pembrolizumab AEOSI when combining pembrolizumab with chemotherapy.

In KEYNOTE-966, the proportion of participants in the pembrolizumab plus chemotherapy group who experienced 1 or more AEs that led to discontinuation of any study treatment was generally similar compared with the placebo plus chemotherapy group (26.1% vs 22.8%).

Safety in special populations was described. The safety findings in the pembrolizumab plus chemotherapy group of KEYNOTE-966 based on age, sex, or ECOG performance status were generally consistent with the established safety profile of pembrolizumab monotherapy and the known safety profile of chemotherapy.

Age: The AE profile based on age in the pembrolizumab plus chemotherapy group was generally consistent with the RSD. The AE profile in the pembrolizumab plus chemotherapy group was generally similar between participants who were <65 years and those ≥65 years with the exception of Grade 3 to 5 drug-related AEs, SAEs, and pembrolizumab dose modifications, which were more frequent in participants ≥65 years of age. A similar pattern was observed between the age groups in the Pooled Combination Dataset (with the exception of Grade 3 to 5 drug-related AEs) and the RSD.

The AE profile between age categories <65 years, 65 to 74 years, and ≥75 years was generally similar in the pembrolizumab plus chemotherapy group, with the exception of SAEs (all causality and drug-related), deaths due to AEs, chemotherapy dose modifications, and discontinuations due to AEs, which were more frequent in participants ≥75 years of age compared with those <65 years or 65 to 74 years. The summary of AEs by age groups (<65, 65 to 74, and ≥75 years) in the results section shows that the proportion of participants in the pembrolizumab plus chemotherapy group who experienced AEs related to falling and cardiovascular events were generally comparable across age groups. Infections, cerebrovascular events, and central nervous system events were more frequent in the ≥75-year age group. Due to the relatively small number of participants in the ≥75-year age group, these results should be interpreted with caution.

Sex: The overall safety profile was similar in male and female individuals, with higher frequency of SAE reported in males.

ECOG status: Similarly, safety was comparable in ECOG 0 vs 1, with higher rates of SAEs in ECOG 1, which might be expected.

Region: No remarkable differences were reported across geographical regions.

Hepatic events of clinical interest (HECI) were specifically analysed in KEYNOTE-966, given the risk of hepatic events in patients with BTC. Reassuringly, in KEYNOTE-966, the rate of HECI was generally similar in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups (9.3% vs 10.7%); further, there were no reported events of AEOSI such as cholangitis sclerosing, autoimmune cholangitis, or immune-mediated cholangitis in the pembrolizumab plus chemotherapy group, and no cases of viral hepatitis flare were observed. The majority of HECI events were of CTCAE Grade 1 to 2 toxicity. The proportion of participants with Grade 3 to 5 HECI were similar in the pembrolizumab plus chemotherapy group (9.1%) and the placebo plus chemotherapy (9.7%). Most HECI were resolved or resolving in both intervention groups. The median time to onset of the first HECI was 88.0 days (range 3 to 711 days) in the pembrolizumab plus chemotherapy group and 146.0 (range 2 to 579 days) in the placebo plus chemotherapy group.

Nevertheless, the MAH was requested to further investigate the relation of hepatic events with biliary stent in view of the previous findings of TOPAZ-1 study and the corresponding warning in the SmPC for Imfinzi. The additional data provided showed that cholangitis and biliary infections are commonly and expectedly increased in the presence of a biliary drainage. The MAH reported that such an increase is 3 to 4-fold than in the lack of any drainage. While limited by the low number of patients in this subgroup analysis is acknowledged, still the risk of biliary complications appears higher when patients have a biliary drainage in the pembrolizumab rather than in the control arm (39% vs 29%) (see Table 63). In addition,

the consistency with a very similar study may reinforce the finding. A warning has been included in section 4.4 of the SmPC to reflect the findings over the rate of biliary complications in patients with biliary stent and drains.

The MAH reported the rate of AEs separately for subjects with liver metastasis at the study enrolment. There is no increase of the liver specific AEs, including AEOSI or severe events.

The AEs leading to **treatment interruption** in the KEYNOTE-966 are consistent with the established safety profile of pembrolizumab monotherapy, chemotherapy and/or underlying BTC. The incremental toxicity when compared with RSD is expected when adding chemotherapy to pembrolizumab.

The drug-related AEs leading to treatment interruption in the KEYNOTE-966 treatment groups are consistent with the established safety profile of pembrolizumab monotherapy and the known safety profile of chemotherapy. The incremental toxicity when compared with the RSD is expected when adding chemotherapy to pembrolizumab.

2.5.2. Conclusions on clinical safety

The safety profile of pembrolizumab in combination with cisplatin and gemcitabine for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults in KEYNOTE-966 study overall is consistent with the established safety profiles of pembrolizumab monotherapy, the chemotherapy doublet and the underlying BTC disease. No new safety concerns were identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The MAH submitted an updated RMP version (41.0 date of final sign off November 2023) with this application. The (main) proposed RMP changes were the following:

Addition of a new indication for pembrolizumab in combination with gemcitabine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

Addition of study KEYNOTE-966 in Modules SIII, SVII, and SVIII; no changes to the risk profile in Modules SIII, SVII, and SVIII.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 41.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 41.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Safety Concern	**Risk Minimisation Measure**	**Pharmacovigilance Activities**
Important Potential Risks: Immune-Related Adverse Reactions		
Immune-related adverse reactions	Routine risk minimisation measures: • The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	Additional risk minimisation measures: • Patient card	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: • For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and	Routine pharmacovigilance activities Additional pharmacovigilance including:

	appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	• Safety monitoring in the ongoing HL trial (KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: • GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: no changes of the package leaflet are foreseen impacting the safe use of the medicinal product.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is: KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

The BTC comprises a heterogeneous group of malignancies affecting the biliary tree that are distinguished based on the anatomical localisation (gallbladder, intrahepatic, perihilar, and distal/periampullary). Given the rare frequency of these tumours, the different subtypes are generally pooled together although carrying different epidemiology, risk factors, clinical presentation, molecular features, and prognosis (Manne *et al*, 2021)[8].

[8]Manne, A., Woods, E., Tsung, A. and Mittra, A. (2021) 'Biliary tract cancers: treatment updates and future directions in the era of precision medicine and immuno-oncology', Frontiers in Oncology, 11, pp. 1-16. doi: 10.3389/fonc.2021.768009.

3.1.2. Available therapies and unmet medical need

Chemotherapy has long been the SoC for first-line treatment of advanced BTC, and the cisplatin – gemcitabine doublet is the most common therapy adopted in the advanced stage of cancer. On 16 December 2022, durvalumab in combination with gemcitabine and cisplatin was approved for the treatment of BTC based on a modest survival advantage compared to chemotherapy alone as observed in the TOPAZ-1 study (EMEA/H/C/004771/II/0046). This combination is recommended as first-line treatment of advanced BTC (ESMO 2023). However, prognosis remains extremely poor with a median OS below 1 year in treated patients (Valle *et al*., 2010)[9], which makes the BTC a condition of significant unmet medical need.

3.1.3. Main clinical studies

The current procedure is supported by one single pivotal phase III double-blind randomized KEYNOTE-966 study comparing the efficacy and safety of pembrolizumab in combination with gemcitabine plus cisplatin to placebo in combination with gemcitabine plus cisplatin.

3.2. Favourable effects

- Pembrolizumab, in addition to gemcitabine plus cisplatin, provided advantage compared to placebo in addition to gemcitabine plus cisplatin on the primary endpoint OS (HR=0.83; 95% CI: 0.72, 0.95; p=0.0034), with a gain in median survival of 1.8 months (12.7 vs 10.9).
- Subgroup analysis demonstrated consistency across most of the prespecified subgroups: age, geographic region, locally advanced vs metastatic, ECOG PS, biliary stent/biliary drain, antibiotics within 1 month of study start, smoking status, prior chemotherapy, PD-L1 expression (CPS>=1 vs <1), PD-L1 expression (CPS <10 vs >=10), MSS, hepatitis B status, subsequent therapies.

3.3. Uncertainties and limitations about favourable effects

- The survival gain exerted by pembrolizumab over placebo was modest, with a 1.8 month increase in median OS compared to placebo.
- PFS did not meet statistical significance, although it showed a trend towards improvement in the experimental vs the control arm (HR=0.86; 95% CI: 0.75, 1; p=0.0225) at IA1 that was confirmed at the FA (HR=0.87; 95% CI: 0.76, 0.99; p=0.0171).
- It was observed a lower performance of pembrolizumab in OS for the gallbladder (HR=0.96; 95% CI: 0.73, 1.26) and extrahepatic (HR=0.99; 95% CI: 0.73, 1.35) tumour, compared to the intrahepatic cancer (HR=0.76; 95% CI:0.64,0.91). Due to the availability of limited clinical data and poor knowledge, no firm conclusions can be derived on the reasons and biological plausibility underlying inconsistency in treatment effect across tumour locations. Considering the absence of a detrimental effect in these subgroups, it can be concluded that a positive B/R of pembrolizumab in association to chemotherapy applies regardless of anatomical classification.
- The screen failure rate was higher than expected, mostly associated with inappropriate organ function as defined by the inclusion criteria. This questions the external representativeness of the study for the target population. The main reason for screen failure was concomitant disease-

[9] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721. PMID: 20375404.

associated liver dysfunction at baseline. Although gemcitabine administration is not contraindicated in patients with liver dysfunction, it needs to be carefully monitored due to the anticipated liver toxicity. In order to inform the treating physicians, a statement including the specifications for liver function of patients enrolled in KEYNOTE-966 has been included in section 5.1 of the SmPC.

3.4. Unfavourable effects

- Treatment-related serious AEs were higher in subjects receiving pembrolizumab plus chemotherapy compared to chemotherapy alone (22.9% vs 15.7%). Pruritus, rash and pyrexia were more common in patients receiving pembrolizumab.
- Grade 3 to 5 adverse events occurred in a comparable proportion in the two study arms (85.3% vs 84.1%). The most frequently reported Grade 3 to 5 AEs (incidence ≥5%) in the pembrolizumab plus chemotherapy group were neutrophil count decreased, anaemia, platelet count decreased, WBC count decreased, and cholangitis.
- Deaths due to drug-related AEs were reported in 1.5% of the pembrolizumab plus chemotherapy group and 0.6% of the placebo plus chemotherapy group.
- The proportion of participants in the pembrolizumab plus chemotherapy group who experienced 1 or more AEs that led to discontinuation of any study treatment was generally similar compared with the placebo plus chemotherapy group (26.1% vs 22.8%).
- The frequency, severity, and types of AEOSI observed in the pembrolizumab plus chemotherapy group were generally consistent with pembrolizumab used as a single agent.
- Patients aged 65-year or older experienced more drug-related AEs and SAEs, resulting in a higher proportion of treatment discontinuations.
- The rate of HECI was generally similar in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups (9.3% vs 10.7%).

3.5. Uncertainties and limitations about unfavourable effects

- The assessment of safety in patients aged ≥75 years is hampered by the low number of patients in this age group (68 vs 57). In the SmPC, a general warning that pembrolizumab in combination with chemotherapy should be used with caution in patients ≥75 years after careful consideration of the potential benefit/risk on an individual basis is already included (see SmPC 5.1).
- With the addition of pembrolizumab, the rate of hepatic events (cholangitis and biliary infections) furtherly increased in patients with biliary stents/drainage (39% vs 29%). A warning to closely monitor patients with biliary stents/drainage has been included in section 4.4 of the SmPC.

3.6. Effects Table

Table 67 Effects table for KEYTRUDA in combination with cisplatin and gemcitabine in KEYNOTE-966 study (data cut-off: 15-DEC-2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	duration of survival from randomization to death regardless	months (95%	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)	Subgroup analysis showed inconsistent effect	CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	of cause	CI)			across relevant BTC subtypes	
PFS	duration of survival without progression from randomization to PD or death whichever occurred first	months (95% CI)	6.5 (5.7, 6.9)	5.6 (4.9, 6.5)	Did not meet statistical significance / Trend maintained in IA1 and FA	
ORR	Confirmed CR + PR	%	29.3	28.4	Did not meet statistical significance	
DoR	Duration of CR/PR until documented PD	months (95% CI)	8.3 (1.2+ -33.0+)	6.8 (1.1+ - 30.0+)		
Unfavourable Effects						
summary	G3-5 AEs	%	71.3	69.3	safety profile consistent with the known safety profile of pembrolizumab in combination with chemotherapy	
	SAE	%	52.2	49.3		
	Discontinuation due to AEs	%	26.1	22.8		
	AEOSI Hypothyroidism Pneumonitis Hyperthyroidism	%	22.1 8.7 4.9 3.6	12.9 2.6 1.9 1.9		
	HECI	%	9.3	10.7		

Abbreviations: AE= adverse event; SAE=serious adverse event; AEOSI= adverse event of special interest; IRR=infusion related reaction; CRS=clinical study report; HECI= Hepatic events of clinical interest

Notes: not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Pembrolizumab, as add-on therapy to gemcitabine+cisplatin for the first-line treatment of locally advanced unresectable or metastatic BTC, provided advantage in OS compared to gemcitabine+cisplatin alone (HR=0.83; 95% CI: 0.72,0.95; p=0.0034). However, only a modest effect in terms of gain in median survival was obtained (i.e. 1.8 months; 12.7 vs 10.9). This finding is similar to what was observed with drugs of the same class in the same setting (durvalumab plus gemcitabine+cisplatin in the TOPAZ-1 trial). The secondary endpoint PFS showed a trend towards improvement in the experimental arm relative to control that did not meet statistical significance (HR=0.86; 95% CI:0.75,1; p=0.0225) at IA1, that was confirmed at the FA (HR=0.87; 95% CI: 0.76, 0.99; p=0.0171). The ORR was unchanged by pembrolizumab treatment (28.7% vs 28.5% in the pembrolizumab and placebo arm, respectively at IA1; 29.3% vs 28.4% in the pembrolizumab and placebo arm, respectively at FA), although a slightly longer duration of response was achieved in the experimental arm compared to control (9.7 vs 6.9 months at IA1; 8.3 vs 6.8 months at FA). The pre-specified subgroup analysis showed a lower performance of pembrolizumab in OS for the gallbladder (HR=0.96; 95% CI: 0.73, 1.26) and extrahepatic (HR=0.99; 95% CI: 0.73, 1.35) tumours, compared to the intrahepatic subtype (HR=0.76; 95% CI: 0.64, 0.91). The PFS and ORR followed the same trend, with PFS reaching a HR>1 in the extrahepatic localisation, and ORR showing even disadvantage of pembrolizumab vs placebo in the extrahepatic and gallbladder cancer sites. However, considering the limited value of subgroup analyses and the absence of a detrimental effect in these subgroups based on OS data, it can be concluded that a favourable effect of pembrolizumab in association to chemotherapy applies regardless of primary tumour location.

Overall, the safety profile of pembrolizumab in KEYNOTE-966 study is consistent with the established toxicity of pembrolizumab monotherapy, the chemotherapy doublet and the underlying BTC disease. No new safety concerns were identified.

3.7.2. Balance of benefits and risks

The benefit/risk ratio of pembrolizumab, as add-on therapy to gemcitabine+cisplatin for the first-line treatment of locally advanced unresectable or metastatic BTC, is considered positive.

3.7.3. Additional considerations on the benefit risk balance

None.

3.8. Conclusions

The overall B/R of KEYTRUDA is positive as add-on therapy to gemcitabine+cisplatin for the first-line treatment of locally advanced unresectable or metastatic BTC.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include KEYTRUDA in combination with gemcitabine and cisplatin for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults, based on final results from study KEYNOTE-966; this is 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. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 41.0 of the RMP has also been submitted.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that KEYTRUDA is not similar to Pemazyre, Tibsovo and Lytgobi within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.