Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Biliary tract cancers, which arise from the intrahepatic or extrahepatic bile ducts and the gallbladder, generally have a poor prognosis and are rising in incidence worldwide. The standard-of-care treatment for advanced biliary tract cancer is chemotherapy with gemcitabine and cisplatin. Because most biliary tract cancers have an immune-suppressed microenvironment, immune checkpoint inhibitor monotherapy is associated with a low objective response rate. We aimed to assess whether adding the immune checkpoint inhibitor pembrolizumab to gemcitabine and cisplatin would improve outcomes compared with gemcitabine and cisplatin alone in patients with advanced biliary tract cancer.

Methods KEYNOTE-966 was a randomised, double-blind, placebo-controlled, phase 3 trial done at 175 medical centres globally. Eligible participants were aged 18 years or older; had previously untreated, unresectable, locally advanced or metastatic biliary tract cancer; had disease measurable per Response Evaluation Criteria in Solid Tumours version 1.1; and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Eligible participants were randomly assigned (1:1) to pembrolizumab 200 mg or placebo, both administered intravenously every 3 weeks (maximum 35 cycles), in combination with gemcitabine (1000 mg/m² intravenously on days 1 and 8 every 3 weeks; no maximum duration) and cisplatin (25 mg/m² intravenously on days 1 and 8 every 3 weeks; maximum 8 cycles). Randomisation was done using a central interactive voice-response system and stratified by geographical region, disease stage, and site of origin in block sizes of four. The primary endpoint of overall survival was evaluated in the intention-to-treat population. The secondary endpoint of safety was evaluated in the as-treated population. This study is registered at ClinicalTrials.gov, NCT04003636.

Findings Between Oct 4, 2019, and June 8, 2021, 1564 patients were screened for eligibility, 1069 of whom were randomly assigned to pembrolizumab plus gemcitabine and cisplatin (pembrolizumab group; n=533) or placebo plus gemcitabine and cisplatin (placebo group; n=536). Median study follow-up at final analysis was 25·6 months (IQR 21·7–30·4). Median overall survival was 12·7 months (95% CI 11·5–13·6) in the pembrolizumab group versus 10·9 months (9·9–11·6) in the placebo group (hazard ratio 0·83 [95% CI 0·72–0·95]; one-sided p=0·0034 [significance threshold, p=0·0200]). In the as-treated population, the maximum adverse event grade was 3 to 4 in 420 (79%) of 529 participants in the pembrolizumab group and 400 (75%) of 534 in the placebo group; 369 (70%) participants in the pembrolizumab group and 367 (69%) in the placebo group had treatment-related adverse events with a maximum grade of 3 to 4. 31 (6%) participants in the pembrolizumab group and 49 (9%) in the placebo group died due to adverse events, including eight (2%) in the pembrolizumab group and three (1%) in the placebo group who died due to treatment-related adverse events.

Interpretation Based on a statistically significant, clinically meaningful improvement in overall survival compared with gemcitabine and cisplatin without any new safety signals, pembrolizumab plus gemcitabine and cisplatin could be a new treatment option for patients with previously untreated metastatic or unresectable biliary tract cancer.

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Introduction

Biliary tract cancers, a complex group of epithelial malignancies arising from the intrahepatic or extrahepatic bile ducts and gallbladder, have a generally poor prognosis.[1] Risk factors include biliary tract injury secondary to chronic cysts or gallstones, liver fluke infection, and other inflammatory causes such as chronic viral hepatitis and cirrhosis.[1,2] Beyond anatomic

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed and Google Scholar on Feb 11, 2023, for English-language publications of randomised controlled trials published since database inception using the terms "PD-1 inhibitor" OR "PD-L1 inhibitor" OR "immune checkpoint inhibitor" AND "unresectable" OR "metastatic" AND "biliary tract cancer" OR "BTC" OR "cholangiocarcinoma" OR "gallbladder cancer". Several phase 2 trials of immune checkpoint inhibitors for the treatment of biliary tract cancer were identified. The only phase 3 study was the double-blind TOPAZ-1 trial of durvalumab plus gemcitabine and cisplatin versus placebo plus gemcitabine and cisplatin in patients with previously untreated unresectable or metastatic biliary tract cancer or with recurrent disease. Results of TOPAZ-1 showed that durvalumab plus chemotherapy significantly improved overall survival versus placebo plus chemotherapy and that the two treatment groups had similar safety profiles.

Added value of this study

To our knowledge, KEYNOTE-966 is the first placebo-controlled study of a PD-1 inhibitor and the second study of a PD-1 or PD-L1 checkpoint inhibitor to show a statistically significant improvement in overall survival and a manageable safety profile in patients with advanced biliary tract cancer. KEYNOTE-966 offers key findings beyond those of TOPAZ-1, owing to its larger population, enrolment of a greater proportion of participants outside of Asia, the continuation of gemcitabine until disease progression, and more complete ascertainment of important clinical biomarkers such as hepatitis B and C viral status, all of which might affect the generalisability of outcomes to a global patient population.

Implications of all the available evidence

Results of KEYNOTE-966 add to the body of evidence supporting the efficacy and safety of adding immune checkpoint inhibitors targeting PD-1 and PD-L1 to standard-of-care chemotherapy in the treatment of patients with biliary tract cancer. The statistically significant, clinically meaningful overall survival benefit observed in the absence of new safety signals supports the combination of pembrolizumab, gemcitabine, and cisplatin as a potential new first-line treatment option for patients with unresectable locally advanced or metastatic biliary tract cancer.

heterogeneity, biliary tract cancers have substantial molecular heterogeneity, which is influenced by location and cause.[3–5] Although biliary tract cancers are uncommon, accounting for less than 1% of all new cancer cases worldwide,[6] the incidence is rising.[1,2,7]

The chemotherapy combination of gemcitabine and cisplatin was established as the standard-of-care first-line therapy for advanced biliary tract cancer more than 10 years ago on the basis of results of the phase 3 ABC-02 study.[8] In ABC-02, median overall survival was 11·7 months (95% CI 9·5–14·3) for gemcitabine plus cisplatin versus 8·1 months (7·1–8·7) for gemcitabine alone (hazard ratio [HR] 0·64, p<0·001). Despite extensive study, triplet chemotherapy regimens and combinations of targeted therapies and chemotherapy have not improved efficacy compared with gemcitabine and cisplatin.[1,9–11] After disease progression, fluorouracil-based combinations show only modest efficacy.[12,13] Patients with cancers harbouring specific molecular aberrations, including *FGFR2* fusions, *IDH1* mutations, and mismatch repair deficiency, can derive benefit from targeted therapies or immune checkpoint inhibitors based predominantly on activity observed in studies conducted in the second-line or later setting.[1,14,15] Because individual molecular subsets are rare, treatment options are limited to chemotherapy for most patients.

The tumour microenvironment in most biliary tract cancers is characterised by immunosuppressive or immune-excluded features,[4] and response to inhibitors of PD-1 and its ligand, PD-L1, given as monotherapy is correspondingly low.[16–18] Several chemotherapies, including gemcitabine and cisplatin, are known to modulate the immune system through direct immunostimulatory mechanisms, downregulation of the immunosuppressive microenvironment, and increased immunogenicity.[19,20] These immunomodulatory effects provide a strong rationale for combining immunotherapy and chemotherapy, particularly in cancers with an immunosuppressive microenvironment. The randomised, double-blind, phase 3 TOPAZ-1 study of patients with advanced biliary tract cancer showed that adding the PD-L1 inhibitor durvalumab to gemcitabine and cisplatin significantly improved overall survival compared with gemcitabine and cisplatin alone (median overall survival 12·8 months [95% CI 11·1–14·0] in the durvalumab group *vs* 11·5 months [10·1–12·5] in the placebo group; HR 0·80 [95% CI 0·66–0·97]; two-sided p=0·021).[21]

We aimed to assess whether adding the anti-PD-1 monoclonal antibody pembrolizumab to gemcitabine and cisplatin improved efficacy compared with gemcitabine and cisplatin alone as first-line therapy for patients with advanced biliary tract cancer.

Methods

Study design and participants

KEYNOTE-966 was a randomised, double-blind, placebo-controlled, phase 3 study done at 175 medical centres in Asia-Pacific, Europe, North America, and South America (appendix pp 2–4). Individuals were eligible for enrolment if they were aged 18 years or older; had histologically confirmed unresectable locally advanced or metastatic extrahepatic cholangiocarcinoma (including mixed hepatocellular carcinoma and cholangiocarcinoma), gallbladder cancer, or intrahepatic cholangiocarcinoma;

had disease measurable per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 determined by the investigator; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; provided tumour tissue for biomarker assessment; had adequate organ function; and had life expectancy of more than 3 months. The only previous systemic therapy permitted was neoadjuvant or adjuvant therapy completed at least 6 months before the diagnosis of unresectable or metastatic disease. Individuals with past or ongoing hepatitis C virus infection were eligible. Individuals with controlled hepatitis B were eligible, including individuals who were positive for HBsAg or had detectable hepatitis B virus DNA as long as they initiated antiviral therapy at least 4 weeks before starting study therapy and their viral load was less than 100 IU/mL. Individuals were excluded from enrolment if they had ampullary cancer or had active autoimmune disease that required systemic treatment in the previous 2 years. Full eligibility criteria are available in the protocol (appendix). Participants self-reported their sex as female or male at birth.

The study protocol and its amendments, which included changes that affected study design (summarised in the document history section of the protocol [appendix]), were approved by the appropriate local or national ethics body for each participating centre. All participants provided written informed consent. The study was conducted in accordance with the Good Clinical Practice requirements outlined by the International Council on Harmonisation, the ethical principles originating with the Declaration of Helsinki, and all local regulations. Clinically important protocol deviations occurred in 13 participants in the pembrolizumab group and 17 participants in the placebo group; these deviations were related to eligibility criteria, study drug administration and discontinuation criteria, and trial procedures.

Randomisation and masking

Participants were randomly assigned (1:1) to pembrolizumab or placebo (normal saline) by study investigators using a central interactive voice-response system (Almac Clinical Technologies, Souderton, PA, USA) and a randomisation list generated by the study funder. Randomisation was stratified by geographical region (Asia *vs* non-Asia), disease stage (locally advanced *vs* metastatic), and site of origin (extrahepatic *vs* gallbladder *vs* intrahepatic). Participants were randomly assigned in blocks of four per stratum. Participants, investigators, and those collecting or analysing the data, including representatives of the sponsor, were masked to treatment assignment. Pembrolizumab and saline placebo were packaged identically to ensure participants and investigators remained masked to treatment assignment. Local pharmacists were aware of assignments to support treatment preparation. In the event of medical emergency, treatment assignment could be unmasked by contacting an emergency unblinding call centre.

Procedures

Pembrolizumab 200 mg or saline placebo was administered intravenously once every 3 weeks. Gemcitabine 1000 mg/m² and cisplatin 25 mg/m² were administered intravenously on days 1 and 8 of 3-week cycles. All treatment was continued until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent, or other reason, whichever occurred first. Pembrolizumab and placebo were limited to 35 cycles, and cisplatin was limited to eight cycles; there was no limit to the number of cycles of gemcitabine. Participants who discontinued gemcitabine, cisplatin, or both because of unacceptable toxicity could continue pembrolizumab or placebo and vice versa. Participants who stopped all study treatment were followed on-study unless they withdrew consent. Crossover was not permitted. Full details regarding treatment decisions, including guidelines for treatment interruption and discontinuation and dose reductions to manage adverse events (dose reductions of pembrolizumab and placebo were not permitted), are in the protocol (appendix).

The presence of antibodies (IgG) against hepatitis C virus was assessed in blood during screening; hepatitis C viral load was measured if anti-hepatitis C virus antibodies were present. The presence of antibodies (total and IgM) against hepatitis B virus core antibody, hepatitis B viral load, and HBsAg were assessed in blood during screening; guidelines for hepatitis B virus assessment during study treatment are in the protocol (appendix). PD-L1 combined positive score was measured in tumour tissue using PD-L1 IHC 22C3 pharmDx (Agilent Technologies; Carpinteria, CA, USA). Microsatellite instability status was assessed in tumour tissue. The names and locations of the central laboratories that tested hepatitis C virus, hepatitis B virus, PD-L1, and microsatellite instability status are summarised in the appendix (p 8).

Contrast-enhanced CT (preferred) or MRI of the chest, abdomen, and pelvis was done within 4 weeks before randomisation, 6 weeks after first study treatment administration, then every 6 weeks up to week 54 and every 12 weeks thereafter. Contrast-enhanced MRI (preferred) or CT of the brain and whole-body radionuclide bone scans were done as clinically indicated. Imaging was continued until disease progression assessed by RECIST version 1.1 according to masked independent central review, start of new anticancer therapy, death, or withdrawal of consent. Survival was assessed every 12 weeks until death, withdrawal of consent, or study end.

Physical examination and laboratory, haematology, and chemistry analyses were done during screening, regularly during study treatment, and at the end of treatment according to the protocol (appendix). Adverse events and laboratory abnormalities were assessed regularly throughout treatment and up to 30 days after discontinuation (≤90 days for serious adverse events in the absence of new anticancer therapy), classified

according to the Medical Dictionary for Regulatory Activities (version 25.1), and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5). Potentially immune-mediated adverse events and infusion reactions were defined on the basis of a list of terms prepared by the sponsor and considered regardless of attribution to study treatment by the investigator.

Outcomes

The primary endpoint was overall survival, defined as time from randomisation to death due to any cause.

Secondary endpoints were progression-free survival, objective response rate, and duration of response, all assessed according to RECIST version 1.1 per masked independent central review, and safety. Progression-free survival was defined as time from randomisation to first documented progressive disease or death due to any cause, whichever occurred first. Objective response rate was defined as the proportion of participants with a best overall response of complete or partial response. Duration of response was defined as the time from first documented evidence of complete or partial response until disease progression or death due to any cause, whichever occurred first.

Change from baseline to week 18 in the global health status quality-of-life scale of the European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire (EORTC QLQ-C30) was a prespecified exploratory endpoint. The remaining prespecified exploratory endpoints are summarised in the protocol (appendix) and will be reported in future publications.

Statistical analysis

The overall type 1 error rate was strictly controlled at one-sided α=0·025 for all overall survival, progression-free survival, and objective response hypotheses using the graphical method of Maurer and Bretz. All α was initially assigned to test overall survival. Per the multiplicity diagram for α reallocation (appendix p 5), if the overall survival comparison was significant, α was reallocated to test progression-free survival and objective response rate. Within each endpoint, type 1 error control across the first interim analysis (data cutoff, Dec 15, 2021), second interim analysis (data cutoff, May 25, 2022), and final analysis (data cutoff, Dec 15, 2022) was maintained using the minimum α spending strategy with a Lan-DeMets spending function approximating O'Brien-Fleming boundaries. The one-sided p value boundaries for declaring superiority of pembrolizumab plus chemotherapy versus placebo plus chemotherapy were 0·0200 for overall survival, 0·0125 for progression-free survival, and 0·0125 for objective response rate.

With enrolment of 1069 participants, 818 deaths, and two interim analyses and assuming an exponential distribution of HR=1 for the first 2 months and HR=0·75 after 2 months, the study had approximately 93% power to identify a significant overall survival benefit for pembrolizumab plus gemcitabine and cisplatin at one-sided α=0·025. With enrolment of 1069 participants and assuming 786 events at the final progression-free survival analysis and an exponential distribution of HR=1 for the first 2 months and HR=0·7 after 2 months, the study had approximately 92% power to identify a significant progression-free survival benefit for pembrolizumab plus gemcitabine and cisplatin at one-sided α=0·0125. With enrolment of 1069 participants and assuming an objective response rate of 25% in the placebo group, the study had 91% power to detect a true difference in response rate of 10% at one-sided α=0·0125. The prespecified final analysis of progression-free survival and objective response rate was at the first interim analysis. Post hoc analyses of progression-free survival and objective response rate were performed at the final analysis.

Overall survival, progression-free survival, and duration of response were estimated using the Kaplan-Meier method. Timepoints of interest were 12 and 24 months for overall survival, 6 and 12 months for progression-free survival and duration of response at the first interim analysis, and 12 and 24 months for progression-free survival and duration of response at final analysis. Censoring rules for overall survival, progression-free survival, and duration of response are summarised in the appendix (p 9).

Between-group comparisons of overall survival and progression-free survival were assessed using a stratified log-rank test; the magnitude of the treatment difference (ie, the HR and 95% CI) was calculated using a stratified Cox regression model with Efron's method of tie handling and treatment as a covariate. Between-group comparisons of objective response rate were assessed using the stratified Miettinen and Nurminen method with weights proportional to the stratum size. The randomisation stratification factors were applied to the stratified log-rank test, the stratified Cox regression model, and the stratified Miettinen and Nurminen method. To assess consistency of the treatment effect, the protocol prespecified descriptive subgroup analyses based on the stratification factors of geographical region, disease stage, and site of origin, and the demographic and clinical characteristics of age, sex, ECOG performance status, smoking status, antibiotic use within 1 month of study start, biliary stent or drain, previous chemotherapy, previous photodynamic therapy, previous radiotherapy, microsatellite instability status, and PD-L1 combined positive score. An unstratified Cox model with treatment as a covariate was used to calculate the magnitude of the treatment difference in each subgroup category; confidence intervals for subgroup analyses were at the nominal 95% confidence level without adjustment for multiplicity. If the number of participants in a subgroup category was less than 5% of the intention-to-treat population, subgroup analysis was

not done for that category and the subgroup was not shown in the forest plot.

The full statistical analysis plan is available in the protocol (appendix). Efficacy was assessed in the intention-to-treat population (ie, all participants randomly assigned to a treatment group); only those participants with a best overall response of complete or partial response were included in analyses of duration of response. Safety and treatment exposure were assessed in the as-treated population (ie, all randomly assigned participants who received one or more doses of any study treatment). An independent data and safety monitoring committee oversaw the study and assessed efficacy and safety at prespecified interim analyses. After reviewing overall survival results from the first and second interim analyses, the independent monitoring committee reported that superiority for the pembrolizumab group was not achieved and recommended the study continue as planned. Sample size and power calculations were done using R (version 3.6.1 with gsDesign version 3.0-5 and simtrial version 0.1.6 packages). Statistical analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT04003636, and is ongoing but closed to enrolment.

Role of the funding source

In collaboration with the academic authors, authors employed by the study funder contributed to study design, data analysis, data interpretation, and writing of the report. The funder maintained the study database and ensured data were collected according to the protocol.

Results

Between Oct 4, 2019, and June 8, 2021, 1564 patients were screened for eligibility, 1069 of whom were randomly assigned to pembrolizumab plus gemcitabine and cisplatin (pembrolizumab group; n=533) or placebo plus gemcitabine and cisplatin (placebo group; n=536) and included in the intention-to-treat population (figure 1). The as-treated population included 529 participants in the pembrolizumab group (527 participants received one or more doses of all study drugs and two received one or more doses of pembrolizumab and gemcitabine only) and 534 participants in the placebo group (all received one or more doses of all study drugs). Baseline demographics and participant characteristics were generally balanced between treatment groups (table 1). 552 (52%) of 1069 participants were male, 517 (48%) were female, 567 (53%) were younger than 65 years, 486 (45%) were enrolled in Asia, 943 (88%) had metastatic disease at enrolment, and 633 (59%) had tumours of intrahepatic origin (table 1). Eight (2%) participants in the pembrolizumab group and five (1%) participants in the placebo group had mixed hepatocellular carcinoma and cholangiocarcinoma.

Median follow-up at final analysis, defined as time from random assignment to the Dec 15, 2022, data cutoff, was 25·6 months (IQR 21·7–30·4). In the as-treated population, 489 (92%) of 529 participants in the pembrolizumab group and 504 (94%) of 534 participants in the placebo group discontinued treatment, most commonly because of progressive disease (figure 1). Median treatment duration was 6·37 months (IQR 2·79–10·84) in the pembrolizumab group and 5·54 months (2·53–9·69) in the placebo group. Median number of cycles administered was 9 (IQR 4–16) in the pembrolizumab group and 8 (4–14) in the placebo group. A summary of cycles administered by treatment component is in the appendix (p 10). In the intention-to-treat population, 253 (47%) of 533 participants in the pembrolizumab group and 261 (49%) of 536 participants in the placebo group had received one or more subsequent anticancer therapies (appendix p 11).

At final analysis, 414 (78%) of 533 participants in the pembrolizumab group and 443 (83%) of 536 participants

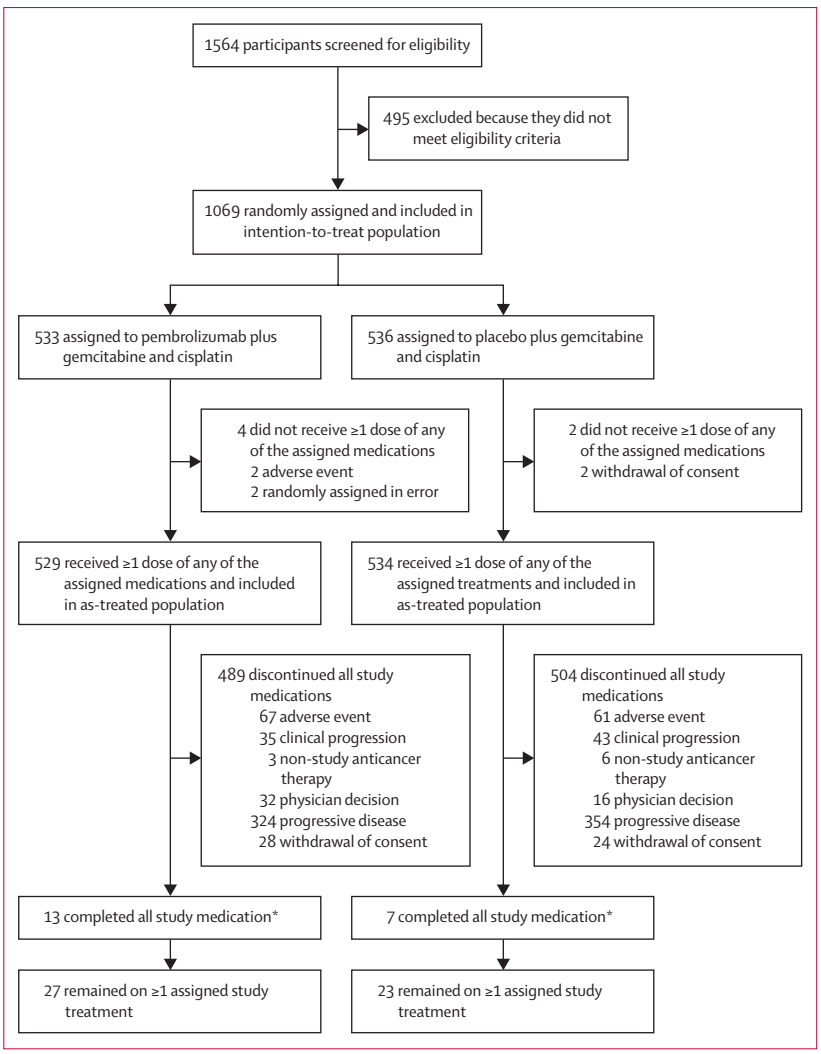


Figure 1: **Trial profile**
*Completed includes participants who received 35 cycles of pembrolizumab or placebo without alternative reason for discontinuation of any drug if given beyond 35 cycles of pembrolizumab or placebo.

	Pembrolizumab plus gemcitabine and cisplatin group (n=533)	Placebo plus gemcitabine and cisplatin group (n=536)
Age, years	64·0 (57·0–71·0)	63·0 (55·0–70·0)
<65	269 (50%)	298 (56%)
≥65	264 (50%)	238 (44%)
Sex		
Female	253 (47%)	264 (49%)
Male	280 (53%)	272 (51%)
Race		
American Indian or Alaskan Native	2 (<1%)	1 (<1%)
Asian	245 (46%)	250 (47%)
Black or African American	11 (2%)	3 (1%)
Multiple	5 (1%)	2 (<1%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	0
White	256 (48%)	268 (50%)
Missing	13 (2%)	12 (2%)
Geographical region		
Asia	242 (45%)	244 (46%)
Not Asia	291 (55%)	292 (54%)
ECOG performance status		
0	258 (48%)	228 (43%)
1	274 (51%)	308 (57%)
≥2	1 (<1%)	0
Site of origin		
Extrahepatic	98 (18%)	105 (20%)
Gallbladder	115 (22%)	118 (22%)
Intrahepatic	320 (60%)	313 (58%)
Disease status		
Locally advanced	60 (11%)	66 (12%)
Metastatic	473 (89%)	470 (88%)
Biliary stent or drain		
No	500 (94%)	495 (92%)
Yes	33 (6%)	41 (8%)
Previous chemotherapy administered as neoadjuvant or adjuvant therapy		
No	483 (91%)	488 (91%)
Yes	50 (9%)	48 (9%)
No previous photodynamic therapy	533 (100%)	536 (100%)
Previous radiotherapy		
No	512 (96%)	508 (95%)
Yes	21 (4%)	28 (5%)
Antibiotic use within 1 month of study start		
No	471 (88%)	493 (92%)
Yes	62 (12%)	43 (8%)
Microsatellite instability status		
Microsatellite instability high	6 (1%)	4 (1%)
Microsatellite stable	433 (81%)	422 (79%)
Unknown	94 (18%)	110 (21%)
Hepatitis B status		
Any viral hepatitis B*	164 (31%)	165 (31%)
Chronic infection	14 (3%)	16 (3%)
Clinically resolved infection	150 (28%)	149 (28%)
No viral hepatitis B	366 (69%)	366 (68%)
Missing	3 (1%)	5 (1%)
Hepatitis C status		
Any viral hepatitis C†	19 (4%)	14 (3%)
Active infection	1 (<1%)	1 (<1%)
Previous infection	18 (3%)	13 (2%)
No viral hepatitis C	514 (96%)	520 (97%)
Missing	0	2 (<1%)
PD-L1 combined positive score		
<1	113 (21%)	110 (21%)
≥1	363 (68%)	365 (68%)
Unknown	57 (11%)	61 (11%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *Chronic hepatitis B infection included participants positive for HBsAg or who had hepatitis B DNA ≥20 IU/mL. Clinically resolved hepatitis B infection included participants positive for hepatitis B core antibody and negative for HBsAg with hepatitis B DNA <20 IU/mL. †Chronic hepatitis C infection included participants positive for hepatitis C IgG antibody and a numerical value for hepatitis C virus RNA. Previous hepatitis C infection included participants positive for hepatitis C IgG antibody but undetectable hepatitis C virus RNA.

Table 1: **Baseline demographic and clinical characteristics in the intention-to-treat population**

in the placebo group had died. Median overall survival was 12·7 months (95% CI 11·5–13·6) in the pembrolizumab group and 10·9 months (9·9–11·6) in the placebo group. Estimated 12-month overall survival rates were 52% (95% CI 47–56) in the pembrolizumab group and 44% (40–48) in the placebo group; estimated 24-month overall survival rates were 25% (95% CI 21–29) in the pembrolizumab group and 18% (15–22) in the placebo group (figure 2A). The efficacy boundary for a statistically significant overall survival benefit for the pembrolizumab group was met (HR 0·83 [95% CI 0·72–0·95]; p=0·0034). Descriptive subgroup analysis showed a benefit for the pembrolizumab group in most prespecified subgroups, including those for PD-L1 combined positive score less than 1 and combined positive score of 1 or more (figure 2B).

361 (68%) of 533 participants in the pembrolizumab group and 391 (73%) of 536 participants in the placebo group had a progression-free survival event by the first interim analysis (median follow-up at the Dec 15, 2021, data cutoff was 13·6 months [IQR 9·7–18·4]). Median progression-free survival was 6·5 months (95% CI 5·7–6·9) in the pembrolizumab group and 5·6 months (5·1–6·6) in the placebo group.

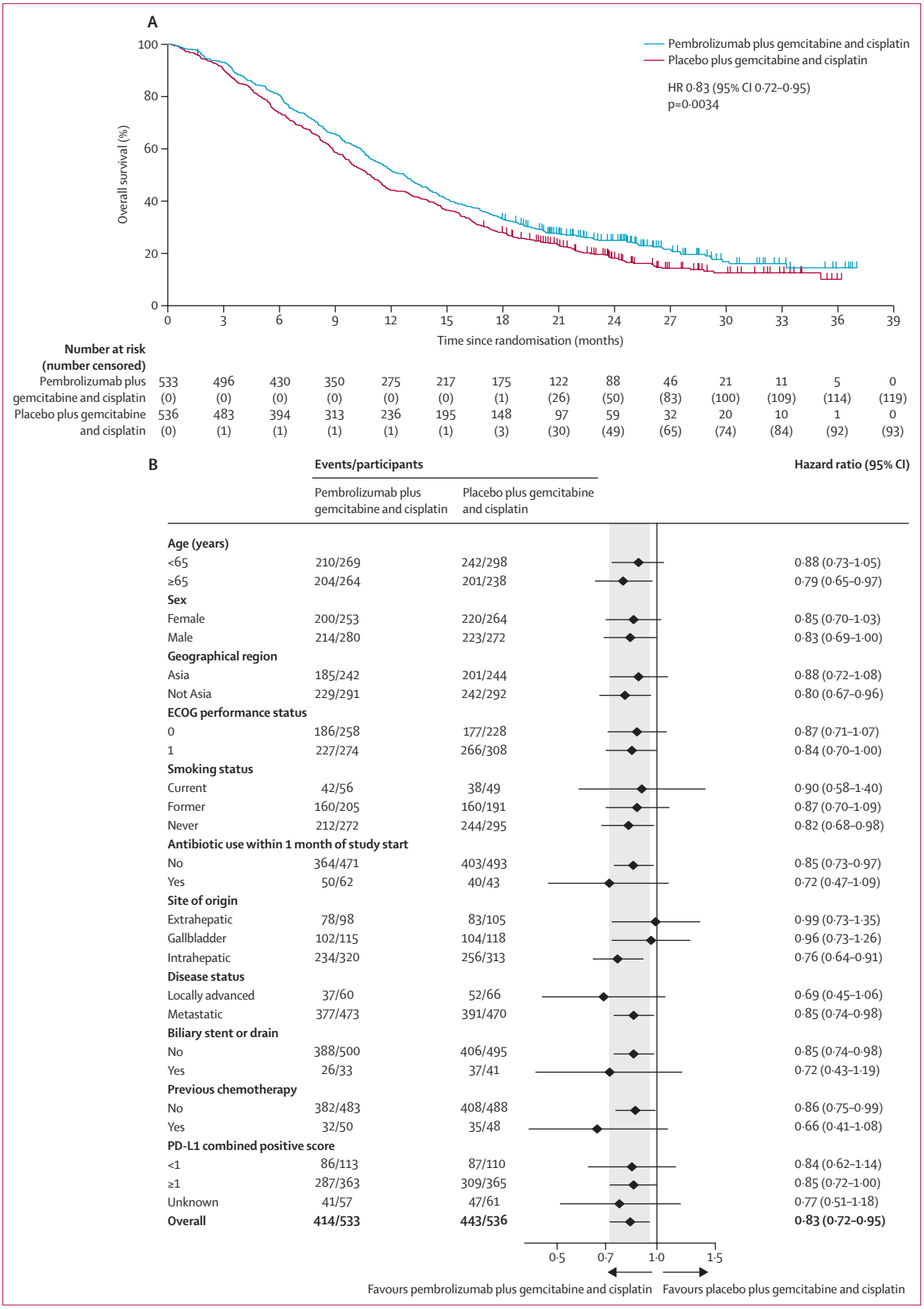


Figure 2: **Overall survival in the intention-to-treat population at the final analysis**

(A) Kaplan-Meier estimates of overall survival; tick marks indicate censored data.

(B) Overall survival in subgroups for which all categories included ≥5% of the intention-to-treat population, with the vertical grey shaded band indicating the 95% CI for the overall population.

The analysis for the overall population 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.

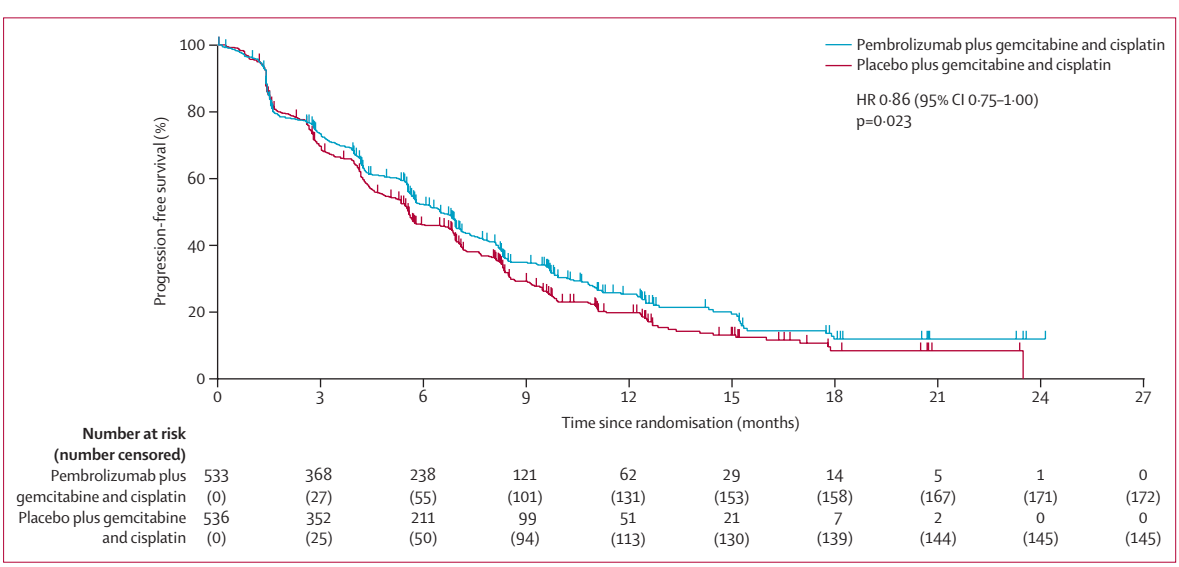
The confidence intervals for the subgroups are at the nominal 95% confidence level without adjustment for multiplicity. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio.

Estimated 6-month progression-free survival was 52% (95% CI 48–57) in the pembrolizumab group and 46% (42–50) in the placebo group; estimated 12-month progression-free survival was 25% (21–30) in the pembrolizumab group and 20% (16–24) in the placebo group (figure 3). The efficacy boundary for a statistically significant progression-free survival benefit for the pembrolizumab group was not met (HR 0·86 [95% CI 0·75–1·00]; p=0·023). A post hoc analysis showed similar outcomes for progression-free survival at the final analysis (HR 0·87 [95% CI 0·76–0·99]; appendix p 6) as at the first interim analyses.

At the first interim analysis, 153 (29% [95% CI 25 to 33]) of 533 participants in the pembrolizumab group and 153 (29% [25 to 33]) of 536 participants in the placebo group had a complete or partial response (table 2). The efficacy boundary for a statistically significant objective response rate benefit for the pembrolizumab group was not met (treatment difference 0·2 percentage points [95% CI −5·2 to 5·6]; p=0·47). Median duration of response was 9·7 months (95% CI 6·9 to 12·2) in the pembrolizumab group and 6·9 months (5·7 to 8·2) in the placebo group. At the final analysis, a post hoc analysis showed objective response rates that were similar to those seen at the first interim analysis (appendix p 7). Estimates of ongoing response at 24 months were 18% (95% CI 11–26) in the pembrolizumab group and 6% (2–13) in the placebo group (appendix pp 7, 12).

In the as-treated population at the final analysis, adverse events of any cause occurred in 524 (99%) of 529 participants in the pembrolizumab group and 532 (<100%) of 534 participants in the placebo group. The maximum toxicity grade was 3 or 4 in 420 (79%) participants in the pembrolizumab group and 400 (75%) participants in the placebo group. Adverse events led to death in 31 (6%) participants in the pembrolizumab group and 49 (9%) participants in the placebo group (appendix p 13). Adverse events led to discontinuation of one or more study drugs in 138 (26%) participants in the pembrolizumab group and in 122 (23%) participants in the placebo group; discontinuation of all study drugs occurred in 35 (7%) participants in the pembrolizumab group and 39 (7%) in the placebo group. Adverse events that occurred in 15% or more of participants in either group are summarised in table 3. No cases of hepatitis B virus-associated hepatitis, defined as hepatitis B virus reactivation plus hepatitis flare by the American Association for the Study of Liver Diseases,[22] were observed.

At the final analysis, treatment-related adverse events occurred in 493 (93%) of 529 participants in the pembrolizumab group, including 369 (70%) with a maximum toxicity of grade 3 or 4, 102 (19%) who discontinued one or more study drugs, and 18 (3%) who discontinued all study drugs. Treatment-related adverse events occurred in 500 (94%) of 534 participants in the placebo group, including 367 (69%) with a grade 3 or 4 event, 81 (15%) who discontinued one or more study drugs, and 14 (3%) who discontinued all study drugs. Treatment-related adverse events led to death in eight (2%) participants in the pembrolizumab group and three (1%) participants in the placebo group (appendix p 14). Treatment-related adverse events that occurred in 50% or more of participants in either treatment group were decreased neutrophil count (321 [61%] participants in the pembrolizumab group and



Number at risk (number censored)										
Pembrolizumab plus gemcitabine and cisplatin	533 (0)	368 (27)	238 (55)	121 (101)	62 (131)	29 (153)	14 (158)	5 (167)	1 (171)	0 (172)
Placebo plus gemcitabine and cisplatin	536 (0)	352 (25)	211 (50)	99 (94)	51 (113)	21 (130)	7 (139)	2 (144)	0 (145)	0 (145)

Figure 3: **Kaplan-Meier estimates of progression-free survival assessed per masked independent central review in the intention-to-treat population at the first interim analysis**

Tick marks indicate censored data. HR=hazard ratio.

320 [60%] participants in the placebo group) and anaemia (278 [53%] and 269 [50%] participants; appendix p 13).

At the final analysis, potentially immune-mediated adverse events and infusion reactions occurred in 117 (22%) of 529 participants in the pembrolizumab group and 69 (13%) of 534 participants in the placebo group, including 37 (7%) in the pembrolizumab group and 21 (4%) in the placebo group who had a grade 3 or 4 adverse event (appendix p 15). The only potentially immune-mediated adverse event that led to death was pneumonitis, which occurred in one (<1%) participant in the pembrolizumab group. 48 (9%) participants in the pembrolizumab group and 26 (5%) participants in the placebo group received systemic corticosteroids to manage immune-mediated adverse events and infusion reactions. Corticosteroid use for individual immune-mediated adverse events is shown in the appendix (p 16). Potentially immune-mediated adverse events that occurred in 5% or more of participants in either group were hypothyroidism (46 [9%] participants in the pembrolizumab group and 14 [3%] participants in the placebo group) and pneumonitis (26 [5%] and ten [2%]; appendix p 15).

Among evaluable participants in the pembrolizumab group (n=518) and placebo group (n=517), least-squares mean change from baseline to week 18 in the global health status quality-of-life scale of the EORTC QLQ-C30 at the final analysis was –2·5 (95% CI –4·5 to –0·5) in both groups (difference in least-square means 0·0 [95% CI –2·5 to 2·6]).

	Pembrolizumab plus gemcitabine and cisplatin group (n=533)	Placebo plus gemcitabine and cisplatin group (n=536)
Objective response rate	153 (29% [95% CI 25–33])	153 (29% [95% CI 25–33])
Disease control rate	399 (75% [95% CI 71–79])	407 (76% [95% CI 72–80])
Best overall response		
Complete response	11 (2%)	7 (1%)
Partial response	142 (27%)	146 (27%)
Stable disease*	246 (46%)	254 (47%)
Progressive disease	102 (19%)	96 (18%)
Not evaluable†	8 (2%)	9 (2%)
Not assessed‡	24 (5%)	24 (4%)
Time to response, months	2·8 (IQR 1·5–4·1)	2·8 (IQR 1·5–4·2)
Duration of response,§ months	9·7 (95% CI 6·9–12·2)	6·9 (95% CI 5·7–8·2)
Extended duration of response§		
≥3 months	93% (95% CI 88–96)	91% (95% CI 85–95)
≥6 months	67% (95% CI 57–74)	56% (95% CI 46–64)
≥9 months	51% (95% CI 41–60)	39% (95% CI 29–48)
≥12 months	41% (95% CI 30–51)	28% (95% CI 19–39)

Data are n (% [95% CI]), n (%), median (IQR) for time to response, median (95% CI) for duration of response, or % (95% CI) for extended duration of response. *Stable disease includes participants with stable disease, non-complete response or non-progressive disease, and no evidence of disease. †Not evaluable includes participants whose post-baseline imaging assessments were not evaluable for best overall response. ‡Not assessed includes participants for whom no post-baseline imaging assessments were available. §Estimated using the Kaplan-Meier method.

Table 2: **Summary of response in the intention-to-treat population at the first interim analysis**

Discussion

In KEYNOTE-966, a randomised, placebo-controlled, phase 3 trial, pembrolizumab plus gemcitabine and cisplatin significantly improved overall survival compared with gemcitabine and cisplatin alone as first-line therapy for patients with unresectable locally advanced or metastatic biliary tract cancer. The overall survival curves did not cross, separated early, and remained separated throughout follow-up, with 24-month survival estimates of 25% in the pembrolizumab group and 18% in the placebo group. Median duration of response was also longer in the pembrolizumab group than in the placebo group (9·7 months *vs* 6·9 months at the first interim analysis). The overall survival benefit of adding pembrolizumab to gemcitabine and chemotherapy was generally consistent across most prespecified subgroups, including those based on geographical region and disease cause. Descriptive subgroup analyses should be interpreted with caution because they were not adjusted for multiplicity and the trial was not powered to compare outcomes in individual subgroups.

To our knowledge, KEYNOTE-966 is the first global phase 3 study of a PD-1 inhibitor, and the second global study overall, to show a significant overall survival improvement in patients with biliary tract cancer. Following from the TOPAZ-1 trial, KEYNOTE-966 validates the role of immune checkpoint inhibitors that target PD-1 and PD-L1 in combination with chemotherapy for treating advanced biliary tract cancer. KEYNOTE-966 and TOPAZ-1 are similar in many aspects, but there are several differences. One difference is the gemcitabine duration. In TOPAZ-1, gemcitabine was limited to eight cycles,[21] whereas in KEYNOTE-966, gemcitabine could be given until disease progression or intolerable toxicity, with no maximum number of cycles. Overall, 43% of participants in the pembrolizumab group and 39% of participants in the placebo group received nine or more cycles of gemcitabine, including 32% in the pembrolizumab group and 27% in the placebo group who received 12 or more cycles. The different gemcitabine durations in KEYNOTE-966 and TOPAZ-1 reflect heterogeneity of clinical practice and provide complementary data that accommodate different standards of care worldwide. KEYNOTE-966 stratified randomisation by geographical region, whereas TOPAZ-1 did not. Furthermore, KEYNOTE-966 enrolled more participants (n=1069 *vs* n=685 in TOPAZ-1), including a larger proportion of participants outside of Asia (583 [55%] *vs* 311 [45%]).[21] It is reassuring that in KEYNOTE-966, the relative benefit of pembrolizumab plus gemcitabine and cisplatin in the large non-Asian population was similar to that observed in the intention-to-treat population. There was more complete ascertainment of biomarkers in KEYNOTE-966 than in TOPAZ-1, including PD-L1 and

	Pembrolizumab plus gemcitabine and cisplatin group (n=529)				Placebo plus gemcitabine and cisplatin group (n=534)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	73 (14%)	287 (54%)	133 (25%)	31 (6%)	83 (16%)	270 (51%)	130 (24%)	49 (9%)
Decreased neutrophil count	73 (14%)	167 (32%)	90 (17%)	0	74 (14%)	171 (32%)	82 (15%)	0
Anaemia	171 (32%)	150 (28%)	2 (<1%)	0	159 (30%)	150 (28%)	4 (1%)	0
Nausea	221 (42%)	12 (2%)	0	0	234 (44%)	12 (2%)	0	0
Decreased platelet count	117 (22%)	64 (12%)	30 (6%)	0	105 (20%)	67 (13%)	40 (7%)	0
Fatigue	161 (30%)	25 (5%)	1 (<1%)	0	150 (28%)	22 (4%)	0	0
Constipation	184 (35%)	2 (<1%)	0	0	187 (35%)	3 (1%)	0	0
Decreased appetite	137 (26%)	6 (1%)	1 (<1%)	0	140 (26%)	15 (3%)	0	0
Decreased white blood cell count	80 (15%)	57 (11%)	4 (1%)	0	80 (15%)	44 (8%)	3 (1%)	0
Pyrexia	127 (24%)	12 (2%)	0	0	99 (19%)	5 (1%)	0	0
Vomiting	108 (20%)	14 (3%)	0	0	121 (23%)	7 (1%)	0	0
Diarrhoea	92 (17%)	11 (2%)	0	0	87 (16%)	10 (2%)	0	1 (<1%)
Abdominal pain	82 (16%)	10 (2%)	0	0	103 (19%)	19 (4%)	0	0
Rash	87 (16%)	3 (1%)	0	0	47 (9%)	2 (<1%)	0	0
Increased aspartate aminotransferase	72 (14%)	16 (3%)	0	0	77 (14%)	19 (4%)	2 (<1%)	0
Increased alanine aminotransferase	75 (14%)	12 (2%)	0	0	99 (19%)	14 (3%)	0	0
Hypomagnesaemia	74 (14%)	5 (1%)	0	0	73 (14%)	5 (1%)	1 (<1%)	0
Pruritus	77 (15%)	0	0	0	51 (10%)	0	0	0
Asthenia	64 (12%)	10 (2%)	1 (<1%)	0	76 (14%)	19 (4%)	0	0
Peripheral oedema	73 (14%)	0	0	0	78 (15%)	7 (1%)	0	0

Data are n (%).

Table 3: **Adverse events of any cause that occurred in ≥15% of participants in either treatment group in the as-treated population at the final analysis**

viral hepatitis status, which provides greater confidence in the use of the treatment combination in patient groups with and without these key covariates. The shape of the overall survival curves and the time they separated was different between the two studies. In KEYNOTE-966, the curves separated in favour of the pembrolizumab group at approximately month 2 after randomisation and maintained a relatively consistent separation over time. In TOPAZ-1, the curves crossed and did not separate in favour of the durvalumab group until approximately month 6 after randomisation and the relative benefit in the durvalumab group seemed to increase with longer follow-up. For regions where gemcitabine continuation is standard of care, it is reassuring that the benefit of adding pembrolizumab is maintained beyond month 6. A notable similarity between KEYNOTE-966 and TOPAZ-1 is the absence of a relationship between higher PD-L1 expression and improved outcomes with chemoimmunotherapy. This is despite the use of different PD-L1 assays and scoring methods in the two studies.[21] The lack of relationship between PD-L1 expression and outcomes with chemoimmunotherapy has been observed in other tumour types, including non-small-cell lung cancer.[23]

Although numerically different, progression-free survival did not differ significantly with pembrolizumab plus gemcitabine and cisplatin compared with placebo plus gemcitabine and cisplatin at the first interim analysis of KEYNOTE-966, which was the prespecified final analysis of progression-free survival. The curves separated around month 3 after randomisation and remained separated in a post hoc analysis at the protocol-specified final analysis. Assessing progression-free survival in patients with biliary tract cancers is complex and often relies on non-radiographic factors, such as biliary obstruction, liver function, and serum carbohydrate antigen 19-9 expression. Thus, progression-free survival assessed per RECIST version 1.1 might not be the best measure of progression-free survival in patients with biliary tract cancer. There was also no difference between treatment groups in objective response rate. The objective response rate in the placebo group was higher than that observed in TOPAZ-1[21] but similar to that observed for gemcitabine and cisplatin in other recent studies.[24,25] Responses in the pembrolizumab group were more durable than those in the placebo group, with 18% of responders in the pembrolizumab group and 6% of responders in the placebo group estimated to be alive and without progressive disease at 24 months at the final analysis.

The adverse event profile of pembrolizumab plus gemcitabine and cisplatin was as expected based on the known profiles of the individual treatment components, and the incidence of adverse events was generally similar between groups. The most common adverse events were blood count-related abnormalities, nausea, and fatigue—events known to be associated with chemotherapy. As

expected, potentially immune-mediated adverse events were more common in the pembrolizumab group. These events were manageable with appropriate supportive therapy. The use of systemic corticosteroids to manage immune-mediated adverse events was generally low (used by <10% of participants in the as-treated population). Health-related quality of life was maintained when pembrolizumab was added to gemcitabine and cisplatin.

Limitations of this study include the disproportionately larger enrolment of participants with intrahepatic tumours compared with population frequencies,[1,7] resulting in smaller sample sizes for patients with extrahepatic cholangiocarcinoma and gallbladder cancer, which could affect subgroup analyses. A bias in favour of patients with intrahepatic tumours has been observed in other studies, including TOPAZ-1,[21] and might reflect the rising incidence of intrahepatic cholangiocarcinoma worldwide.[1,7] The requirement for tumour tissue at study entry might have also contributed to a selection bias for patients with intrahepatic tumours because these tumours are more accessible for sampling. Given the low prevalence of microsatellite instability-high biliary tract tumours,[26–30] we were unable to assess outcomes by microsatellite instability status because only ten participants with known microsatellite instability-high tumours were enrolled. Samples for biomarker assessment were collected from consenting participants, and translational analyses are ongoing. A dedicated analysis of complete patient-reported outcomes data will be presented in the future.

In conclusion, KEYNOTE-966 met its primary endpoint as pembrolizumab plus gemcitabine and cisplatin resulted in a statistically significant, clinically meaningful improvement in overall survival compared with gemcitabine and cisplatin alone without new safety signals in participants with previously untreated metastatic or unresectable biliary tract cancer. Pembrolizumab plus gemcitabine and cisplatin could be a new treatment option for this population.

Contributors

RKK, RSF, JF, ZR, JWV, LY, UM, ABS, and AV participated in the conception, design, and planning of the study. RKK, CY, RSF, JF, ZR, SLC, JWV, JE, and AV served on the study advisory committee. RKK, MU, CY, RSF, JF, ZR, TY, H-JK, SLC, MO, CV, MB, JOP, OB, UP, JWV, JE, and AV enrolled and treated participants and acquired data. LY performed the statistical analysis. RKK, MU, RSF, LY, UM, ABS, and AV analysed and interpreted the data. RKK, LY, UM, and ABS accessed and verified the study data. All authors had access to the data, provided critical review of the manuscript, and approved the submitted draft. All authors vouch for data accuracy and completeness, fidelity of the study to the protocol and its amendments, and study conduct in accordance with Good Clinical Practice guidelines. All authors had responsibility for the final decision to submit for publication.

Declaration of interests

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Data sharing

Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the USA and EU or after product development is discontinued. Circumstances might prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an SAS portal so that the requestor can perform the proposed analyses.

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