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**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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2

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

6

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46

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54

## 55 **Summary**

56 **Background:** Biliary tract cancers, which arise from the intrahepatic or extrahepatic bile ducts  
57 and the gallbladder, generally have a poor prognosis and are rising in incidence worldwide. The  
58 standard-of-care treatment for advanced biliary tract cancer has been chemotherapy with  
59 gemcitabine and cisplatin. Because most biliary tract cancers have an immune-suppressed  
60 microenvironment, immune checkpoint inhibitor monotherapy is associated with a low objective  
61 response rate. We conducted a study to determine whether adding the immune checkpoint  
62 inhibitor pembrolizumab to gemcitabine and cisplatin would improve outcomes compared with  
63 gemcitabine and cisplatin alone in biliary tract cancer.

64

65 **Methods:** The randomised, double-blind, placebo-controlled phase 3 KEYNOTE-966 study  
66 enrolled participants with previously untreated unresectable, locally advanced or metastatic  
67 biliary tract cancer at 175 medical centres globally. Eligible participants were randomised (1:1)  
68 to pembrolizumab 200 mg or placebo, both administered intravenously every 3 weeks  
69 (maximum, 35 cycles), in combination with gemcitabine (1000 mg/m<sup>2</sup> intravenously on days 1  
70 and 8 every 3 weeks; no maximum duration) and cisplatin (25 mg/m<sup>2</sup> intravenously on days 1  
71 and 8 every 3 weeks; maximum, 8 cycles). Randomisation was stratified by geographic region,  
72 disease stage, and site of origin. The primary endpoint of overall survival was evaluated in the  
73 intention-to-treat population. The secondary endpoint of safety was evaluated in the as-treated  
74 population. This study is registered at ClinicalTrials.gov, number NCT04003636.

75

76 **Findings:** Between October 4, 2019, and June 8, 2021, 1069 participants were randomised to  
77 pembrolizumab plus gemcitabine and cisplatin (pembrolizumab group; n=533) or placebo plus  
78 gemcitabine and cisplatin (placebo group; n=536). Median study follow-up at final analysis was

79 25·6 months (IQR 21·7-30·4). Median overall survival was 12·7 months (95% confidence  
80 interval [CI] 11·5-13·6) in the pembrolizumab group versus 10·9 months (95% CI 9·9-11·6) in  
81 the placebo group (hazard ratio 0·83 [95% CI 0·72-0·95], one-sided  $p=0·0034$  [significance  
82 threshold,  $p=0·0200$ ]). In the as-treated population, the maximum adverse event grade was 3-4  
83 in 420 (79%) of 529 participants in the pembrolizumab group and 400 (75%) of 534 in the  
84 placebo group and was grade 5 in 31 (6%) and 49 (9%) participants, respectively.

85

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

90

91 **Funding:** Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

92

93 **Panel: Research in Context**

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

105  
106 **Added value of this study:** KEYNOTE-966 is the first placebo-controlled study of a PD-1  
107 inhibitor and the second study of a PD-1/PD-L1 pathway inhibitor to show a statistically  
108 significant improvement in overall survival and a manageable safety profile in patients with  
109 advanced biliary tract cancer. KEYNOTE-966 offers key findings beyond those of TOPAZ-1  
110 owing to its larger population, enrolment of a greater proportion of participants outside of Asia,  
111 the continuation of gemcitabine until disease progression, and more complete ascertainment of  
112 important clinical biomarkers such as hepatitis B and C viral status, all of which may impact the  
113 generalizability of outcomes to a global patient population.

114  
115 **Implications of all the available evidence:** Results of KEYNOTE-966 add to the body of  
116 evidence supporting the efficacy and safety of adding immune checkpoint inhibitors targeting  
117 the PD-1/PD-L1 pathway to standard-of-care chemotherapy in the treatment of biliary tract  
118 cancer. The statistically significant, clinically meaningful overall survival benefit observed in the

119 absence of new safety signals supports the combination of pembrolizumab, gemcitabine, and  
120 cisplatin as a potential new first-line treatment option for patients with unresectable locally  
121 advanced or metastatic biliary tract cancer.  
122

123 **Introduction**

124 Biliary tract cancers, a complex family of epithelial malignancies arising from the intrahepatic or  
125 extrahepatic bile ducts and gallbladder, have a generally poor prognosis.<sup>1</sup> Risk factors include  
126 biliary tract injury secondary to chronic cysts or gallstones, liver fluke infection, and other  
127 inflammatory aetiologies such as chronic viral hepatitis and cirrhosis.<sup>1,2</sup> Beyond anatomic  
128 heterogeneity, biliary tract cancers demonstrate substantial molecular heterogeneity, which is  
129 influenced by location and aetiology.<sup>3-5</sup> Although biliary tract cancers are uncommon, accounting  
130 for <1% of all new cancer cases worldwide,<sup>6</sup> the incidence is rising.<sup>1,2,7</sup>

131  
132 The chemotherapy combination of gemcitabine and cisplatin was established as the standard-  
133 of-care first-line therapy for advanced biliary tract cancer more than ten years ago based on  
134 results of the phase 3 ABC-02 study.<sup>8</sup> In ABC-02, median overall survival was 11·7 months for  
135 gemcitabine plus cisplatin versus 8·1 months for gemcitabine alone (hazard ratio [HR] 0·64,  
136  $p < 0·001$ ). Despite extensive study, triplet chemotherapy regimens and combinations of targeted  
137 therapies and chemotherapy do not improve efficacy compared with gemcitabine and  
138 cisplatin.<sup>1,9-11</sup> After disease progression, 5-fluorouracil-based combinations demonstrate only  
139 modest efficacy.<sup>12,13</sup> Patients with cancers harbouring specific molecular aberrations, including  
140 *FGFR2* fusions, *IDH1* mutations, and mismatch repair deficiency, can derive benefit from  
141 targeted therapies or immune checkpoint inhibitors based predominantly on activity observed in  
142 studies conducted in the second-line or later setting.<sup>1,14,15</sup> Because individual molecular subsets  
143 are rare, treatment options are limited to chemotherapy for most patients.

144  
145 The tumour microenvironment in most biliary tract cancers is characterized by  
146 immunosuppressive or immune-excluded features,<sup>4</sup> and response to inhibitors of programmed  
147 cell death protein 1 (PD-1) and its ligand, PD-L1, given as monotherapy is correspondingly  
148 low.<sup>16-18</sup> Several chemotherapies, including gemcitabine and cisplatin, are known to modulate



149 the immune system through direct immunostimulatory mechanisms, downregulation of the  
150 immunosuppressive microenvironment, and increased immunogenicity.<sup>19,20</sup> These  
151 immunomodulatory effects provide a strong rationale for combining immunotherapy and  
152 chemotherapy, particularly in cancers with an immunosuppressive microenvironment. The  
153 randomised, double-blind, phase 3 TOPAZ-1 study of patients with advanced biliary tract cancer  
154 showed that adding the PD-L1 inhibitor durvalumab to gemcitabine and cisplatin significantly  
155 improved overall survival compared with gemcitabine and cisplatin alone (median overall  
156 survival 12·8 months in the durvalumab group vs 11·5 months in the placebo group; HR 0·80  
157 [95% CI 0·66-0·97]; two-sided p=0·021).<sup>21</sup>

158

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

162

## 163 **Methods**

### 164 *Study Design and Participants*

165 KEYNOTE-966 is a randomised, double-blind, placebo-controlled phase 3 study done at 175  
166 medical centres in Asia-Pacific, Europe, North America, and South America (appendix pp 2-4).  
167 Individuals were eligible for enrolment if they were aged  $\geq 18$  years, had histologically confirmed  
168 unresectable locally advanced or metastatic extrahepatic cholangiocarcinoma (including mixed  
169 hepatocellular carcinoma and cholangiocarcinoma), gallbladder cancer, or intrahepatic  
170 cholangiocarcinoma, had disease measurable per Response Evaluation Criteria in Solid Tumors  
171 (RECIST) version 1.1 determined by the investigator, had Eastern Cooperative Oncology Group  
172 (ECOG) performance status 0 or 1, provided tumour tissue for biomarker assessment, had  
173 adequate organ function, and had life expectancy  $> 3$  months. The only prior systemic therapy  
174 permitted was neoadjuvant or adjuvant therapy completed  $\geq 6$  months before the diagnosis of

175 unresectable or metastatic disease. Individuals with past or ongoing hepatitis C virus (HCV)  
176 infection were eligible. Individuals with controlled hepatitis B were eligible; this included  
177 individuals who were positive for hepatitis B serum antigen (HBsAg) or had detectable hepatitis  
178 B virus (HBV) DNA as long as they initiated antiviral therapy  $\geq 4$  weeks before starting study  
179 therapy and their viral load was  $< 100$  IU/mL. Individuals were excluded from enrolment if they  
180 had ampullary cancer or had active autoimmune disease that required systemic treatment in the  
181 previous two years. Full eligibility criteria are available in the protocol (appendix). Participants  
182 self-reported their sex as female or male at birth.

183  
184 The study protocol and its amendments, which included changes that affected study design  
185 (summarized in the “Document History” section of the protocol [appendix]), were approved by  
186 the appropriate local or national ethics body for each participating centre. All participants  
187 provided written informed consent. The study was conducted in accordance with the Good  
188 Clinical Practice requirements outlined by the International Council on Harmonisation, the  
189 ethical principles originating with the Declaration of Helsinki, and all local regulations. Clinically  
190 important protocol deviations occurred in 13 participants in the pembrolizumab group and 17  
191 participants in the placebo group; these deviations were related to eligibility criteria, study drug  
192 administration and discontinuation criteria, and trial procedures.

193

#### 194 *Randomisation and masking*

195 Participants were randomised (1:1) to pembrolizumab or placebo by study investigators using a  
196 central interactive voice-response system (Almac Clinical Technologies, Souderton, PA, USA)  
197 and a randomisation list generated by the study funder. Randomisation was stratified by  
198 geographic region (Asia vs non-Asia), disease stage (locally advanced vs metastatic), and site  
199 of origin (extrahepatic vs gallbladder vs intrahepatic). Participants were randomised in blocks of  
200 4 per stratum. Participants, investigators, and those collecting or analysing the data, including

201 representatives of the sponsor, were masked to treatment assignment. Local pharmacists were  
202 aware of assignments to support treatment preparation. In the event of medical emergency,  
203 treatment assignment could be unmasked by contacting an emergency unblinding call centre.  
204

#### 205 *Procedures*

206 Pembrolizumab 200 mg or saline placebo was administered intravenously once every three  
207 weeks. Gemcitabine 1000 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup> were administered intravenously on  
208 days one and eight of three-week cycles. All treatment was continued until disease progression,  
209 unacceptable toxicity, investigator decision, withdrawal of consent, or other reason, whichever  
210 occurred first; pembrolizumab and placebo were limited to 35 cycles, and cisplatin was limited to  
211 eight cycles. Participants who discontinued gemcitabine, cisplatin, or both because of  
212 unacceptable toxicity could continue pembrolizumab or placebo and vice versa. Participants  
213 who stopped all study treatment were followed on-study unless they withdrew consent.

214 Crossover was not permitted. Full details regarding treatment decisions, including guidelines for  
215 treatment interruption and discontinuation and dose reductions to manage adverse events (dose  
216 reductions of pembrolizumab and placebo not permitted), are found in the protocol (appendix).

217  
218 The presence of antibodies (IgG) against HCV was determined in blood during screening; HCV  
219 viral load was determined if anti-HCV antibodies were present. The presence of antibodies (total  
220 and IgM) against hepatitis B core antibody, HBV viral load, and HBsAg were determined in  
221 blood during screening; guidelines for HBV assessment during study treatment are available in  
222 the protocol (appendix). PD-L1 combined positive score (CPS) was determined in tumour tissue  
223 using PD-L1 IHC 22C3 pharmDx (Agilent Technologies; Carpinteria, CA, USA). Microsatellite  
224 instability (MSI) status was assessed in tumour tissue. The names and locations of the central  
225 laboratories that tested HCV, HBV, PD-L1, and MSI status are summarized in the appendix (p  
226 8).

227

228 Contrast-enhanced computed tomography (preferred) or magnetic resonance imaging of the  
229 chest, abdomen, and pelvis was performed within 4 weeks before randomisation, 6 weeks after  
230 first study treatment administration, then every 6 weeks through week 54 and every 12 weeks  
231 thereafter. Contrast-enhanced magnetic resonance imaging (preferred) or computed  
232 tomography of the brain and whole-body radionuclide bone scans were performed as clinically  
233 indicated. Imaging was continued until disease progression assessed by RECIST version 1.1  
234 according to masked independent central review, start of new anticancer therapy, death, or  
235 withdrawal of consent. Survival was assessed every 12 weeks until death, withdrawal of  
236 consent, or study end.

237

238 Physical examination and laboratory, haematology, and chemistry analyses were done during  
239 screening, regularly during study treatment, and at the end of treatment according to the  
240 protocol (appendix). Adverse events and laboratory abnormalities were assessed regularly  
241 throughout treatment and up to 30 days after discontinuation ( $\leq 90$  days for serious events in the  
242 absence of new anticancer therapy), classified according to the *Medical Dictionary for*  
243 *Regulatory Activities*, version 25.1, and graded according to the National Cancer Institute  
244 Common Terminology Criteria for Adverse Events, version 5. Potentially immune-mediated  
245 adverse events and infusion reactions were based on a list of terms prepared by the sponsor  
246 and considered regardless of attribution to study treatment by the investigator.

247

#### 248 *Outcomes*

249 The primary endpoint was overall survival, defined as time from randomisation to death due to  
250 any cause. Secondary endpoints were progression-free survival, objective response rate, and  
251 duration of response, all assessed according to RECIST version 1.1 per masked independent  
252 central review, and safety. Progression-free survival was defined as time from randomisation to

253 first documented progressive disease or death due to any cause, whichever occurred first.  
254 Objective response rate was defined as the proportion of participants with a best overall  
255 response of complete or partial response. Duration of response was defined as the time from  
256 first documented evidence of complete or partial response until disease progression or death  
257 due to any cause, whichever occurred first. Change from baseline to week 18 in the global  
258 health status/quality of life scale of the European Organisation for Research and Treatment of  
259 Cancer 30-Item Core Quality of Life Questionnaire (EORTC QLQ-C30) was a prespecified  
260 exploratory endpoint. The remaining prespecified exploratory endpoints are summarized in the  
261 protocol (appendix) and will be presented in future publications.

262

### 263 *Statistical Analysis*

264 The overall type 1 error rate was strictly controlled at one-sided  $\alpha=0.025$  for all overall survival,  
265 progression-free survival, and objective response hypotheses using the graphical method of  
266 Maurer and Bretz. All alpha was initially assigned to test overall survival. Per the multiplicity  
267 diagram for alpha re-allocation (appendix p 5), if the overall survival comparison was significant,  
268 alpha was reallocated to test progression-free survival and objective response rate. Within each  
269 endpoint, type 1 error control across the interim and final analyses was maintained using the  
270 minimum alpha spending strategy with a Lan-DeMets spending function approximating O'Brien-  
271 Fleming boundaries. The one-sided p-value boundaries for declaring superiority of  
272 pembrolizumab plus chemotherapy versus placebo plus chemotherapy were 0.0200 for overall  
273 survival, 0.0125 for progression-free survival, and 0.0125 for objective response rate.

274 With enrolment of 1069 participants, based on a target of 818 deaths and two interim analyses  
275 and assuming an exponential distribution of HR=1 for the first two months and HR=0.75 after  
276 two months, the study had approximately 93% power to identify a significant overall survival  
277 benefit for pembrolizumab plus gemcitabine and cisplatin at one-sided  $\alpha=0.025$ . With enrolment  
278 of 1069 participants, based on a target of 786 events at the final progression-free survival

279 analysis and assuming an exponential distribution of HR=1 for the first two months and HR=0.7  
280 after two months, the study had approximately 92% power to identify a significant progression-  
281 free survival benefit for pembrolizumab plus gemcitabine and cisplatin at one-sided  $\alpha=0.0125$ .  
282 With enrolment of 1069 participants and assuming an objective response rate of 25% in the  
283 placebo group, the study had 91% power to detect a true difference in response rate of 10% at  
284 one-sided  $\alpha=0.0125$ . The prespecified final analysis of progression-free survival and objective  
285 response rate was at the first interim analysis. Post hoc analyses of progression-free survival  
286 and objective response rate were performed at the final analysis.

287

288 Overall survival, progression-free survival, and duration of response were estimated using the  
289 Kaplan-Meier method. Timepoints of interest were 12 and 24 months for overall survival, 6 and  
290 12 months for progression-free survival and duration of response at the first interim analysis,  
291 and 12 and 24 months for progression-free survival and duration of response at final analysis.  
292 Censoring rules for overall survival, progression-free survival, and duration of response are  
293 summarised in the appendix (p 9).

294

295 Between-group comparisons of overall survival and progression-free survival were assessed  
296 using a stratified log-rank test; the magnitude of the treatment difference (i.e., the HR and 95%  
297 CI) was calculated using a stratified Cox regression model with Efron's method of tie handling  
298 and treatment as a covariate. Between-group comparisons of objective response rate were  
299 assessed using the stratified Miettinen and Nurminen method with weights proportional to the  
300 stratum size. The randomisation stratification factors were applied to the stratified log-rank test,  
301 the stratified Cox regression model, and the stratified Miettinen and Nurminen method. To  
302 assess consistency of the treatment effect, the protocol prespecified descriptive subgroup  
303 analyses based on the stratification factors and other demographic and clinical characteristics.  
304 An unstratified Cox model with treatment as a covariate was used to calculate the magnitude of

305 the treatment difference in each subgroup category; confidence intervals for subgroup analyses  
306 were at the nominal 95% confidence level without adjustment for multiplicity. If the number of  
307 participants in a subgroup category was <5% of the intention-to-treat population, subgroup  
308 analysis was not performed for that category and the subgroup was not displayed in the forest  
309 plot.

310

311 The full statistical analysis plan is available in the protocol (appendix). Efficacy was assessed in  
312 the intention-to-treat population (ie, all participants randomised to a treatment group; only those  
313 participants with a best overall response of complete or partial response were included in  
314 analyses of duration of response. Safety and treatment exposure were assessed in the as-  
315 treated population (ie, all randomised participants who received  $\geq 1$  dose of any study  
316 treatment). An independent data and safety monitoring committee oversaw the study and  
317 assessed efficacy and safety at prespecified interim analyses. After reviewing overall survival  
318 results from the first and second interim analyses, the independent monitoring committee  
319 reported that superiority for the pembrolizumab group was not achieved and recommended the  
320 study continue as planned. Sample size and power calculations were performed using R  
321 (version 3.6.1 with “gsDesign” version 3.0-5 and “simtrial” version 0.1.6 packages). Statistical  
322 analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov  
323 (number NCT04003636) and is ongoing but closed to enrolment.

324

#### 325 *Role of the funding source*

326 In collaboration with the academic authors, authors employed by the study funder contributed to  
327 study design, data analysis, data interpretation, and writing this report. The funder maintained  
328 the study database and ensured data were collected according to the protocol. All authors had  
329 access to the data and vouch for data accuracy and completeness, fidelity of the study to the

330 protocol and its amendments, and study conduct in accordance with Good Clinical Practice  
331 guidelines.

332

### 333 **Results**

334 Between October 4, 2019, and June 8, 2021, 1069 participants were randomised to  
335 pembrolizumab plus gemcitabine and cisplatin (pembrolizumab group; n=533) or placebo plus  
336 gemcitabine and cisplatin (placebo group; n=536) and included in the intention-to-treat  
337 population (figure 1). The as-treated population included 529 participants in the pembrolizumab  
338 group (n=527 who received  $\geq 1$  dose of all study drugs and n=2 who received  $\geq 1$  dose of  
339 pembrolizumab and gemcitabine only) and 534 participants in the placebo group (all  
340 received  $\geq 1$  dose of all study drugs). Baseline demographics and participant characteristics  
341 were generally balanced between treatment groups (table 1). Overall, 552 (52%) of 1069  
342 participants were male, 567 (53%) were aged <65 years, 486 (45%) were enrolled in Asia, 943  
343 (88%) had metastatic disease at enrolment, and 633 (59%) had tumours of intrahepatic origin  
344 (table 1). Eight (2%) participants in the pembrolizumab group and five (1%) participants in the  
345 placebo group had mixed hepatocellular carcinoma and cholangiocarcinoma.

346

347 Median study follow-up at final analysis, defined as time from randomisation to the December  
348 15, 2022, data cutoff, was 25.6 months (IQR 21.7-30.4). In the as-treated population, 489 (92%)  
349 of 529 participants in the pembrolizumab group and 504 (94%) of 534 participants in the  
350 placebo group discontinued treatment, most commonly because of progressive disease (figure  
351 1). Median treatment duration was 6.37 months (IQR 2.79-10.84) in the pembrolizumab group  
352 and 5.54 months (IQR 2.53-9.69) in the placebo group. Median number of cycles administered  
353 was 9.00 (IQR 4.00-16.00) and 8.00 (IQR 4.00-14.00), respectively. A summary of cycles  
354 administered by treatment component is in the appendix (p 10). In the intention-to-treat



355 population, 253 (47%) of 533 participants in the pembrolizumab group and 261 (49%) of 536  
356 participants in the placebo group received  $\geq 1$  subsequent anticancer therapy (appendix p 11).

357  
358 At final analysis, 414 (78%) of 533 participants in the pembrolizumab group and 443 (83%) of  
359 536 participants in the placebo group had died. Median overall survival was 12·7 months (95%  
360 CI 11·5-13·6) in the pembrolizumab group and 10·9 months (95% CI 9·9-11·6) in the placebo  
361 group; estimated 24-month overall survival rates were 25% (95% CI 21-29) and 18% (95% CI  
362 15-22; figure 2A). The efficacy boundary for declaring a statistically significant overall survival  
363 benefit for the pembrolizumab group was met (HR 0·83 [95% CI 0·72-0·95];  $p=0\cdot0034$ ).

364 Descriptive subgroup analysis showed a benefit for the pembrolizumab group in most  
365 prespecified subgroups, including those for PD-L1 CPS  $<1$  and CPS  $\geq 1$  (figure 2B).

366  
367 With 361 (68%) of 533 participants in the pembrolizumab group and 391 (73%) of 536  
368 participants in the placebo group having experienced a progression-free survival event at the  
369 first interim analysis (median study follow-up as of the December 15, 2021, data cutoff, 13·6  
370 months [IQR 9·7-18·4]), median progression-free survival was 6·5 months (95% CI 5·7-6·9) in  
371 the pembrolizumab group and 5·6 months (95% CI 5·1-6·6) in the placebo group; estimated 12-  
372 month progression-free survival rates were 25% (95% CI 21-30) and 20% (95% CI 16-24; figure  
373 3). The efficacy boundary for declaring a statistically significant progression-free survival benefit  
374 for the pembrolizumab group was not met (HR 0·86 [95% CI 0·75-1·00];  $p=0\cdot023$ ). A post hoc  
375 analysis showed similar outcomes for progression-free survival at the final analysis (HR 0·87  
376 [95% CI 0·76-0·99]; appendix p 6).

377  
378 At the first interim analysis, 153 (29% [95% CI 25-33]) of 533 participants in the pembrolizumab  
379 group and 153 (29% [95% CI 25-33]) of 536 participants in the placebo group had complete or  
380 partial response (table 2). The efficacy boundary for declaring a statistically significant objective

381 response rate benefit for the pembrolizumab group was not met (treatment difference 0·2 [95%  
382 CI -5·2 to 5·6]; p=0·47). Median duration of response was 9·7 months (95% CI 6·9-12·2) in the  
383 pembrolizumab group and 6·9 months (95% CI 5·7-8·2) in the placebo group (appendix p 7). At  
384 final analysis, objective response rates were similar, and 24-month estimates of  
385 ongoing response were 18% in the pembrolizumab group and 6% in the placebo group  
386 (appendix pp 7 and 12).

387

388 In the as-treated population at the final analysis, adverse events of any cause occurred in 524  
389 (99%) of 529 participants in the pembrolizumab group and 532 (<100%) of 534 participants in  
390 the placebo group. The maximum toxicity grade was 3 or 4 in 420 (79%) participants in the  
391 pembrolizumab group and 400 (75%) participants in the placebo group. Adverse events led to  
392 death in 31 (6%) participants in the pembrolizumab group and 49 (9%) participants in the  
393 placebo group (appendix p 13). Adverse events led to discontinuation of  $\geq 1$  study drug in 138  
394 (26%) participants in the pembrolizumab group and in 122 (23%) participants in the placebo  
395 group; discontinuation of all study drugs occurred in 35 (7%) and 39 (7%) participants,  
396 respectively. Adverse events that occurred in  $\geq 10\%$  of participants in either group are  
397 summarized in table 3. No cases of HBV-associated hepatitis, defined as HBV reactivation plus  
398 hepatitis flare by the American Association for the Study of Liver Diseases,<sup>22</sup> were observed.

399

400 Treatment-related adverse events occurred in 493 (93%) of 529 participants in the  
401 pembrolizumab group, including 369 (70%) with a maximum toxicity of grade 3 or 4, 102 (19%)  
402 who discontinued  $\geq 1$  study drug, and 18 (3%) who discontinued all study drugs. Treatment-  
403 related adverse events occurred in 500 (94%) of 534 participants in the placebo group, including  
404 367 (69%) with a grade 3 or 4 event, 81 (15%) who discontinued  $\geq 1$  study drug, and 14 (3%)  
405 who discontinued all study drug. Treatment-related adverse events led to death in 8 (2%)  
406 participants in the pembrolizumab group and 3 (1%) participants in the placebo group (appendix

407 p 14). Treatment-related adverse events that occurred in  $\geq 50\%$  of participants in either  
408 treatment group were decreased neutrophil count (321 [61%] participants in the pembrolizumab  
409 group and 320 [60%] participants in the placebo group) and anaemia (278 [53%] and 269 [50%]  
410 participants, respectively; appendix p 13).

411  
412 Potentially immune-mediated adverse events and infusion reactions occurred in 117 (22%) of  
413 529 participants in the pembrolizumab group and 69 (13%) of 534 participants in the placebo  
414 group, including 37 (7%) in the pembrolizumab group and 21 (4%) in the placebo group who  
415 experienced a grade 3 or 4 event (appendix p 15). The only potentially immune-mediated event  
416 that led to death was pneumonitis that occurred in 1 ( $<1\%$ ) participant in the pembrolizumab  
417 group. 48 (9%) participants in the pembrolizumab group and 26 (5%) participants in the placebo  
418 group received systemic corticosteroids to manage immune-mediated adverse events and  
419 infusion reactions. Corticosteroid use for individual immune-mediated AEs is in the appendix (p  
420 16). Potentially immune-mediated AEs that occurred in  $\geq 5\%$  of participants in either group were  
421 hypothyroidism (46 [9%] participants in the pembrolizumab group and 14 [3%] participants in the  
422 placebo group) and pneumonitis (26 [5%] and 10 [2%], respectively; appendix p 15).

423  
424 Among evaluable participants in the pembrolizumab (n=518) and placebo (n=517) groups, least-  
425 squares mean change from baseline to week 18 in the global health status/quality of life scale of  
426 the EORTC QLQ-C30 was 2.5 (95% CI -4.5 to -0.5) in both the pembrolizumab and placebo  
427 groups (difference in least-square means 0.0 [95% CI -2.5 to 2.6]).

428

## 429 **Discussion**

430 In the randomised, placebo-controlled phase 3 KEYNOTE-966 study, pembrolizumab plus  
431 gemcitabine and cisplatin significantly improved overall survival compared with gemcitabine and  
432 cisplatin alone as first-line therapy for unresectable locally advanced or metastatic biliary tract

433 cancer. The overall survival curves did not cross, separated early, and remained separated  
434 throughout follow-up, with 24-month survival estimates of 25% in the pembrolizumab group and  
435 18% in the placebo group. Median duration of response was also prolonged in the  
436 pembrolizumab group (9·7 months vs 6·9 months at the first interim analysis). The overall  
437 survival benefit of adding pembrolizumab to gemcitabine and chemotherapy was generally  
438 consistent across most prespecified subgroups, including those based on geographic region  
439 and disease aetiology. There was a trend towards improved benefit with pembrolizumab in  
440 participants with intrahepatic tumour origin, although the 95% CIs for the intrahepatic,  
441 extrahepatic, and gallbladder subgroups overlapped one another and the 95% CI for the  
442 intention-to-treat population. Descriptive subgroup analyses should be interpreted with caution  
443 because they were not adjusted for multiplicity and the trial was not powered to compare  
444 outcomes in individual subgroups.

445  
446 KEYNOTE-966 is only the third global phase 3 study to demonstrate a significant overall  
447 survival improvement in biliary tract cancer. Following on TOPAZ-1, KEYNOTE-966 validates  
448 the role of immune checkpoint inhibitors that target the PD-1/PD-L1 pathway in combination with  
449 chemotherapy for treating advanced biliary tract cancer. KEYNOTE-966 and TOPAZ-1 are  
450 similar in many aspects, but there are several differences. One difference is the gemcitabine  
451 duration. In TOPAZ-1, gemcitabine was limited to eight cycles,<sup>21</sup> whereas in KEYNOTE-966,  
452 gemcitabine could be given until disease progression or intolerable toxicity, with no maximum  
453 number of cycles. Overall, 43% of participants in the pembrolizumab group and 39% of  
454 participants in the placebo group received  $\geq 9$  cycles of gemcitabine, including 32% and 27%,  
455 respectively, who received  $\geq 12$  cycles. The different gemcitabine durations in KEYNOTE-966  
456 and TOPAZ-1 reflect heterogeneity of clinical practice and provide complementary data that  
457 accommodate different standards of care worldwide. KEYNOTE-966 stratified randomisation by  
458 geographic region, whereas TOPAZ-1 did not. Further, KEYNOTE-966 enrolled a larger

459 proportion of participants outside of Asia (55% vs 45% in TOPAZ-1) and a larger number of  
460 participants overall (n=1069 vs n=685).<sup>21</sup> It is reassuring that the relative benefit of  
461 pembrolizumab plus gemcitabine and cisplatin in the large non-Asian population was similar to  
462 that observed in the intention-to-treat population. There was more complete ascertainment of  
463 biomarkers in KEYNOTE-966, including PD-L1 and viral hepatitis status, which provides greater  
464 confidence in the use of the combination in groups with and without these key covariates. The  
465 shape of the overall survival curves and the time they separated was different between the  
466 studies. In KEYNOTE-966, the curves separated in favour of the pembrolizumab group at  
467 approximately month two and maintained a relatively consistent separation over time. In  
468 TOPAZ-1, the curves crossed and did not separate in favour of the durvalumab group until  
469 approximately month six and the relative benefit in the durvalumab group seemed to increase  
470 with longer follow-up. For regions where gemcitabine continuation is standard-of-care, it is  
471 reassuring that the benefit of adding pembrolizumab is maintained beyond month six. A notable  
472 similarity between KEYNOTE-966 and TOPAZ-1 is the lack of a relationship between higher  
473 PD-L1 expression and improved outcomes with chemoimmunotherapy. This is despite the use  
474 of different PD-L1 assays and scoring methods in the two studies.<sup>21</sup> The lack of relationship  
475 between PD-L1 expression and outcomes to chemoimmunotherapy has been observed in other  
476 tumour types, including non-small cell lung cancer.<sup>23</sup>

477

478 There was a trend towards improved progression-free survival with pembrolizumab plus  
479 gemcitabine and cisplatin at the first interim analysis of KEYNOTE-966, which was the  
480 prespecified final analysis of progression-free survival, although the difference was not  
481 statistically significant. The curves separated around month three and remained separated in a  
482 post hoc analysis performed at the protocol-specified final analysis. Assessing progression-free  
483 survival in biliary tract cancers is complex and often relies on non-radiographic factors such as  
484 biliary obstruction, liver function, and serum carbohydrate antigen 19-9 expression. Thus,

485 progression-free survival assessed per RECIST version 1.1 may not be the best measure of  
486 progression-free survival in biliary tract cancer. There was also no difference between treatment  
487 groups in objective response rate. The objective response rate in the placebo group was higher  
488 than that observed in TOPAZ-1<sup>21</sup> but similar to that observed for gemcitabine and cisplatin in  
489 other recent studies.<sup>24,25</sup> Responses in the pembrolizumab group were more durable than those  
490 in the placebo group, with 18% of responders in the pembrolizumab group and 6% of  
491 responders in the placebo group estimated to be alive and without progressive disease at 24  
492 months at the final analysis.

493  
494 The adverse event profile of pembrolizumab plus gemcitabine and cisplatin was as expected  
495 based on the known profiles of the individual treatment components, and the incidence of  
496 adverse events was generally similar between groups. The most common adverse events were  
497 blood count-related abnormalities, nausea, and fatigue, events known to be associated with  
498 chemotherapy. As expected, potentially immune-mediated adverse events were more common  
499 in the pembrolizumab group. These events were manageable with appropriate supportive  
500 therapy. The use of systemic corticosteroids to manage immune-mediated adverse events was  
501 generally low (used by <10% of participants in the as-treated population). Health-related quality  
502 of life was maintained when pembrolizumab was added to gemcitabine and cisplatin.

503  
504 Limitations of this study include the disproportionately larger enrolment of participants with  
505 intrahepatic tumours compared with population frequencies,<sup>1,7</sup> resulting in smaller sample sizes  
506 for extrahepatic cholangiocarcinoma and gallbladder cancer that could impact subgroup  
507 analysis. A bias in favour of intrahepatic tumours has been observed in other studies, including  
508 TOPAZ-1<sup>21</sup> and may reflect the rising incidence of intrahepatic cholangiocarcinoma worldwide.<sup>1,7</sup>  
509 The requirement for tumour tissue at study entry may have also contributed to a selection bias  
510 for intrahepatic tumours because they are more accessible for tumour sampling. Given the low

511 prevalence of MSI-high biliary tract tumours,<sup>26-30</sup> we were unable to assess outcomes by MSI  
512 status because only ten participants with known MSI-high tumours were enrolled. Samples for  
513 biomarker assessment were collected from consenting participants, and translational analyses  
514 are ongoing. A dedicated analysis of complete patient-reported outcomes data will be presented  
515 in the future.

516

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

523

#### 524 **Contributors**

525 RKK, RSF, JF, ZR, JWV, LY, UM, ABS, and AV participated in the conception, design, and  
526 planning of the study. RKK, CY, RSF, JF, ZR, SLC, JWC, JE, and AV served on the study  
527 advisory committee. RKK, MU, CY, RSF, JF, ZR, TY, H-JK, SLC, MO, CV, MB, JOP, OB, UP,  
528 JWV, JE, and AV enrolled and treated participants and acquired data. LY performed the  
529 statistical analysis. RKK, MU, RSF, LY, UM, ABS, and AV analysed and interpreted the data.  
530 RKK, LY, UM, and ABS verified the study data. RKK, MO, CY, RSF, JF, ZR, TY, H-JK, SLC,  
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532 critical review of the manuscript, and approved the submitted draft.

533

#### 534 **Declaration of interests**

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617

## 618 **Data Sharing**

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

639

640

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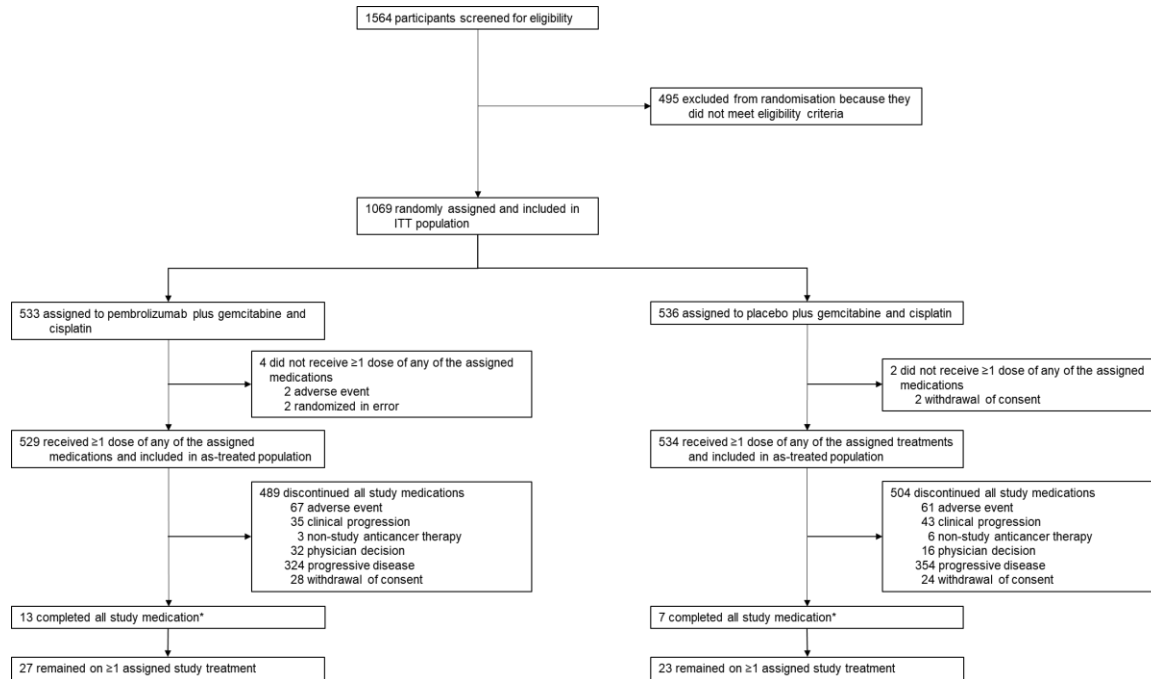
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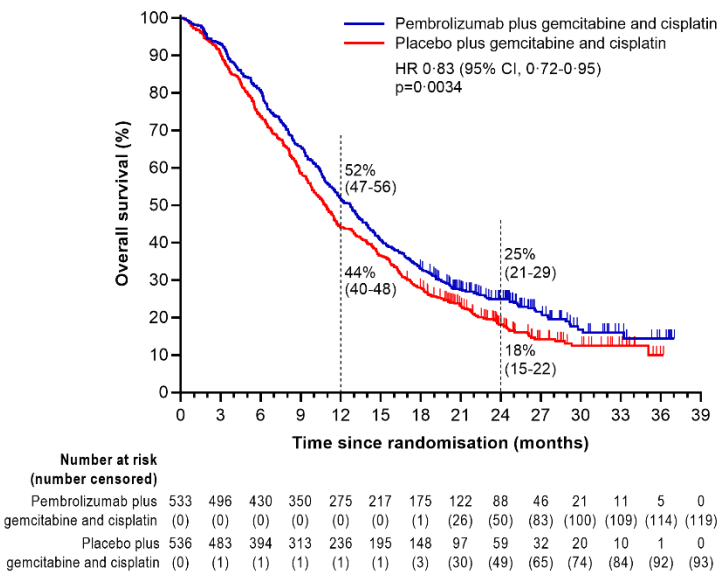
735 **Figure 1. Trial Profile.** \*Completed includes participants who received 35 cycles of  
 736 pembrolizumab or placebo without alternative reason for discontinuation of any drug if given  
 737 beyond 35 cycles of pembrolizumab or placebo.



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740 **Figure 2. Overall survival in the intention-to-treat population at the final analysis. (A)**  
 741 Kaplan-Meier estimates of overall survival; tick marks indicate censored data. (B) Overall  
 742 survival in subgroups for which all categories included  $\geq 5\%$  of the intention-to-treat population,  
 743 with the vertical grey shaded band indicating the 95% CI for the overall population. The analysis  
 744 for the overall population is based on the same stratified Cox regression model as conducted for  
 745 the primary analysis. Subgroup analyses were conducted using an unstratified Cox model with  
 746 treatment as a covariate. The confidence intervals for the subgroups are at the nominal 95%  
 747 confidence level without adjustment for multiplicity. ECOG=Eastern Cooperative Oncology  
 748 Group.

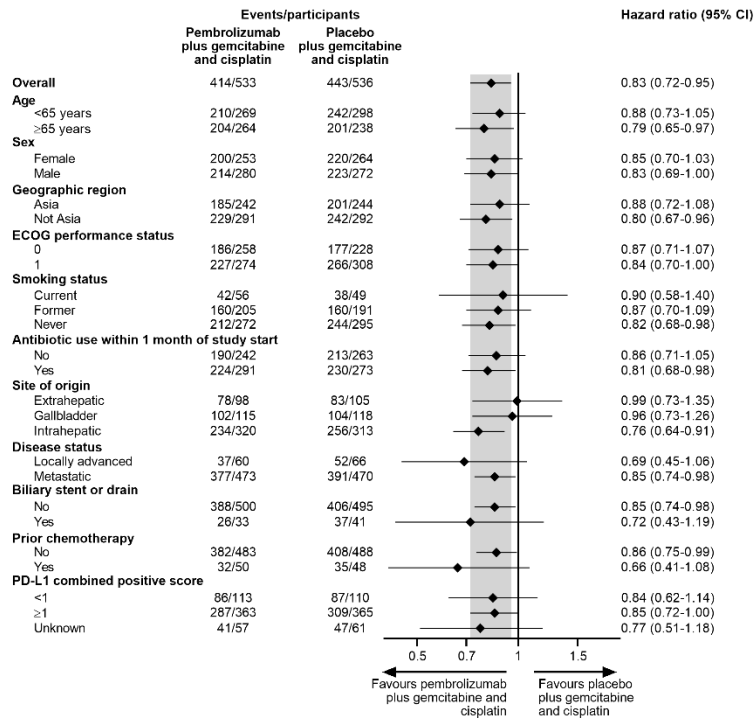
749 **A.**



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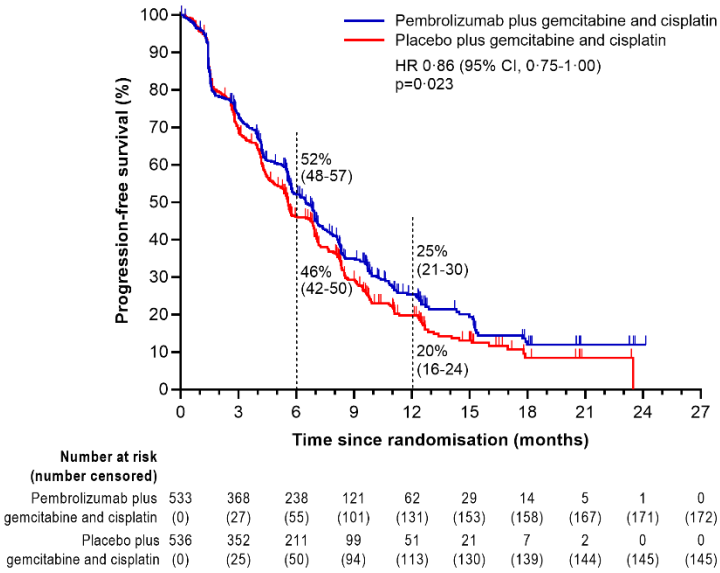
752 B.



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755 **Figure 3. Kaplan-Meier estimates of progression-free survival assessed per masked**  
 756 **independent central review in the intention-to-treat population at the first interim**  
 757 **analysis. Tick marks indicate censored data.**



758

759

760 **Table 1. Baseline demographic and clinical characteristics in the intention-to-treat**  
 761 **population**

	<b>Pembrolizumab plus gemcitabine and cisplatin group (n=533)</b>	<b>Placebo plus gemcitabine and cisplatin group (n=536)</b>
Age, years	64.0 (57.0-71.0)	63.0 (55.0-70.0)
<65	269 (50%)	298 (56%)
≥65	264 (50%)	238 (44%)
<b>Sex</b>		
Female	253 (47%)	264 (49%)
Male	280 (53%)	272 (51%)
<b>Race</b>		
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%)
<b>Geographic region</b>		
Asia	242 (45%)	244 (46%)
Not Asia	291 (55%)	292 (54%)
<b>ECOG performance status</b>		

	<b>Pembrolizumab plus gemcitabine and cisplatin group (n=533)</b>	<b>Placebo plus gemcitabine and cisplatin group (n=536)</b>
0	258 (48%)	228 (43%)
1	274 (51%)	308 (57%)
≥2	1 (<1%)	0
<b>Site of origin</b>		
Extrahepatic	98 (18%)	105 (20%)
Gallbladder	115 (22%)	118 (22%)
Intrahepatic	320 (60%)	313 (58%)
<b>Disease status</b>		
Locally advanced	60 (11%)	66 (12%)
Metastatic	473 (89%)	470 (88%)
<b>Biliary stent or drain</b>		
No	500 (94%)	495 (92%)
Yes	33 (6%)	41 (8%)
<b>Prior chemotherapy administered as neoadjuvant or adjuvant therapy</b>		
No	483 (91%)	488 (91%)
Yes	50 (9%)	48 (9%)
No prior photodynamic therapy	533 (100%)	536 (100%)
<b>Prior radiation therapy</b>		
No	512 (96%)	508 (95%)
Yes	21 (4%)	28 (5%)
<b>Antibiotic use within 1 month of study start</b>		

	<b>Pembrolizumab plus gemcitabine and cisplatin group (n=533)</b>	<b>Placebo plus gemcitabine and cisplatin group (n=536)</b>
No	242 (45%)	263 (49%)
Yes	291 (55%)	273 (51%)
<b>MSI status</b>		
MSI-H	6 (1%)	4 (1%)
MSS	433 (81%)	422 (79%)
Unknown	94 (18%)	110 (21%)
<b>Hepatitis B status</b>		
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%)
<b>Hepatitis C status</b>		
Any viral hepatitis C†	19 (4%)	14 (3%)
Active infection	1 (<1%)	1 (<1%)
Prior infection	18 (3%)	13 (2%)
No viral hepatitis C	514 (96%)	520 (97%)
Missing	0	2 (<1%)
<b>PD-L1 combined positive score</b>		
<1	113 (21%)	110 (21%)
≥1	363 (68%)	365 (68%)

	<b>Pembrolizumab plus gemcitabine and cisplatin group (n=533)</b>	<b>Placebo plus gemcitabine and cisplatin group (n=536)</b>
Unknown	57 (11%)	61 (11%)

762 Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

763 MSI=microsatellite instability. MSI-H=microsatellite instability high. MSS=microsatellite stable.

764 \*Chronic hepatitis B infection included participants positive for hepatitis B surface antigen or

765 who had hepatitis B DNA  $\geq 20$  IU/mL. Clinically resolved hepatitis B infection included

766 participants positive for hepatitis B core antibody and negative for hepatitis B surface antigen

767 with hepatitis B DNA  $< 20$  IU/mL. †Chronic hepatitis C infection included participants positive for

768 hepatitis C IgG antibody and a numeric value for hepatitis C virus RNA. Prior hepatitis C

769 infection included participants positive for hepatitis C IgG antibody but undetectable hepatitis C

770 virus RNA.

771



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

	<b>Pembrolizumab plus gemcitabine and cisplatin group (n=533)</b>	<b>Placebo plus gemcitabine and cisplatin group (n=536)</b>
Objective response rate	153 (29% [25-33])	153 (29% [25-33])
Disease control rate	399 (75% [71-79])	407 (76% [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 (1·5-4·1)	2·8 (1·5-4·2)
Duration of response,§ months	9·7 (6·9-12·2)	6·9 (5·7-8·2)
Extended duration of response§		
≥3 months	93%	91%
≥6 months	67%	56%
≥9 months	51%	39%
≥12 months	41%	28%

774 Data are n (% [95% CI]), n (%), median (IQR) (for time to response), median (95% CI) (for  
 775 duration of response), or %. \*Stable disease includes participants with stable disease, non-  
 776 complete response or non-progressive disease, and no evidence of disease. †Not evaluable

777 includes participants whose post-baseline imaging assessments were not evaluable for best  
778 overall response. ‡Not assessed includes participants for whom no post-baseline imaging  
779 assessments were available. §Estimated using the Kaplan-Meier method.

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

	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

	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
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

	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
Peripheral oedema	73 (14%)	0	0	0	78 (15%)	7 (1%)	0	0

Data are n (%).

## Supplemental Appendix

### Table of Contents

Investigator list .....	2
Figure S1. Multiplicity diagram for alpha re-allocation .....	5
Figure S2. Kaplan-Meier estimates of progression-free survival assessed per masked independent central review in the intention-to-treat population at the final analysis .....	6
Figure S3. Kaplan-Meier analyses of duration of response assessed per masked independent central review in the intention-to-treat population .....	7
Table S1. Central laboratories used in KEYNOTE-966 .....	8
Table S2. Censoring rules for progression-free survival and duration of response .....	9
Table S3. Number of cycles administered for each component of study treatment in treated participants at the final analysis .....	10
Table S4. Summary of subsequent anticancer therapy in the intention-to-treat population at the final analysis.....	11
Table S5. Summary of response in the intention-to-treat population at the first interim analysis and at the final analysis .....	12
Table S6. Adverse events that led to death in the as-treated population at the final analysis .....	13
Table S7. Treatment-related adverse events that occurred in $\geq 5\%$ of participants either treatment group in the safety population at the final analysis .....	14
Table S8. Potentially immune-mediated adverse events and infusion reactions in the as-treated population at the final analysis .....	15
Table S9. Use of corticosteroids for the treatment of potentially immune-mediated adverse events and infusion reactions in participants in the safety population who experienced an event at the final analysis.....	16
Study Protocol .....	17

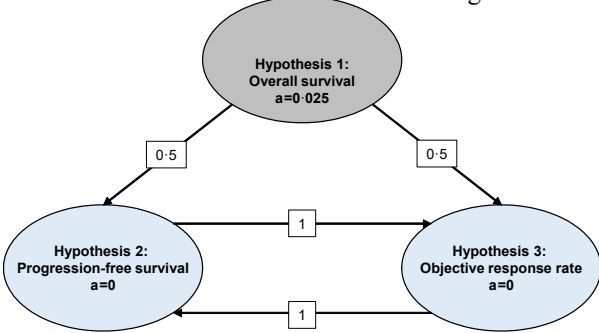
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	Hunan Provincial People Hospital	Peng, Chuang
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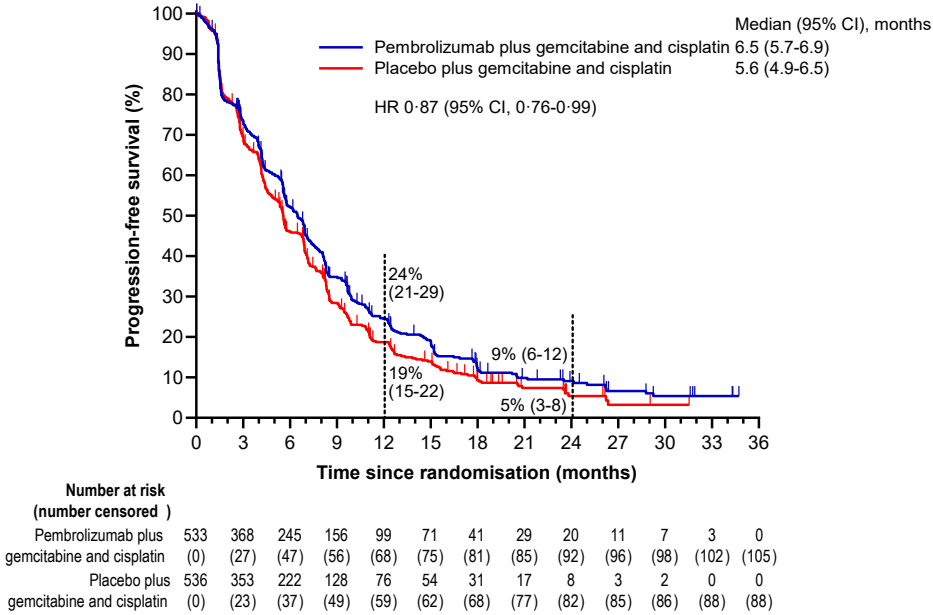


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	Winship Cancer Institute of Emory University	Gbolahan, Olumide (current) Diab, Maria (former) Akce, Mehmet (former)
	University of California Los Angeles - Santa Monica	Finn, Richard
	University of Alabama at Birmingham Comprehensive Cancer Center	Outlaw, Darryl (current) Gbolahan, Olumide (former)
	University of California - San Francisco	Kelley, Robin
	Blue Ridge Cancer Care	Kochenderfer, Mark
	Laura and Isaac Perlmutter Cancer Center at NYU Langone Health	Beri, Nina
	Charleston Oncology	Lingerfelt, Brian
	OHSU Center for Health & Healing	Lopez, Charles
	Northwest Georgia Oncology Centers PC	McCune, Steven
	Saint Francis Health System	Yang, Xuezhong
	Yale University	Stein, Stacey
	University of Oklahoma - Stephenson Oklahoma Cancer Center	Hatoum, Hassan
	Decatur Memorial Hospital	Wade, James
	Hartford Hospital	Elias, Rawad

**Figure S1. Multiplicity diagram for alpha re-allocation.** The initial alpha allocated to each hypothesis is shown under the individual hypotheses. The weights for reallocation should superiority be demonstrated for a hypothesis are shown in the boxes on the lines connecting individual hypotheses.

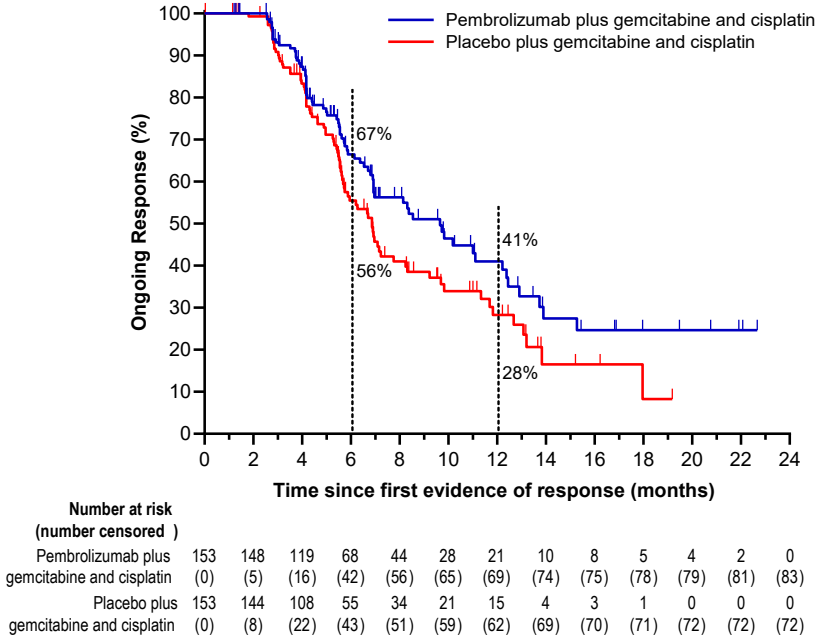


**Figure S2. Kaplan-Meier estimates of progression-free survival assessed per masked independent central review in the intention-to-treat population at the final analysis. Tick marks indicate censored data.**

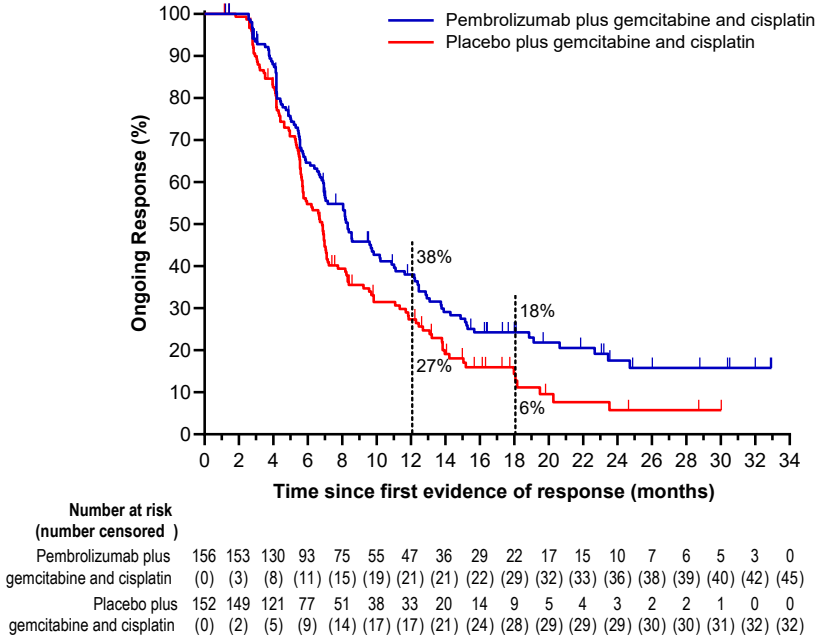


**Figure S3. Kaplan-Meier analyses of duration of response assessed per masked independent central review in the intention-to-treat population.** Tick marks indicate censored data.

**(A) First interim analysis**



**(B) Final analysis**



1 **Table S1. Central laboratories used in KEYNOTE-966.**

Laboratory Assessment	Laboratory Name and Location	Supported Regions
PD-L1 CPS	NeoGenomics Laboratories, Inc., Aliso Viejo, CA, USA	Argentina, Australia, Belgium, Brazil, Canada, Chile, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Malaysia, Netherlands, New Zealand, Republic of Korea, Spain, Taiwan, Thailand, Türkiye, United Kingdom, USA
	Labcorp Pharmaceutical Research and Development (Shanghai) Co., Limited, Shanghai, China	China
MSI status	Almac Diagnostics, LLC, Craigavon, United Kingdom	Argentina, Australia, Belgium, Brazil, Canada, Chile, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Malaysia, Netherlands, New Zealand, Republic of Korea, Spain, Taiwan, Thailand, Türkiye, United Kingdom, USA
	Q2 Solutions (Beijing) Co., Ltd., Beijing, China	China
HBV and HCV*	PPD Laboratories, Highland Heights, KY, USA	Argentina, Brazil, Canada, Chile, USA
	PPD Laboratories, Zaventem, Belgium	Belgium, France, Germany, Ireland, Israel, Italy, Netherlands, Spain, Türkiye, United Kingdom
	PPD Laboratories, Singapore	Australia, Hong Kong, Japan, Malaysia, New Zealand, Republic of Korea, Taiwan, Thailand
	Labcorp Pharmaceutical Research and Development (Shanghai) Co., Limited, Shanghai, China	China

2 HBV=hepatitis B virus. HCV=hepatitis C virus. MSI=microsatellite. PD-L1 CPS=programmed cell death ligand 1 combined positive score. \*HBV and HCV  
3 status were tested locally in 13 participants screened for eligibility due to limitations related to the COVID-19 pandemic.  
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7 **Table S2. Censoring rules for overall survival, progression-free survival, and duration of response.**

<b>Overall survival</b>	<b>Censoring rule</b>
No death date	Censored on the date last known to be alive
<b>Progression-free survival</b>	<b>Date of progression or censoring</b>
PD or death documented after $\leq 1$ missed disease assessment and before new anticancer therapy, if any	Progressed at date of documented PD or death
Death or progression immediately after $\geq 2$ consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of $\geq 2$ consecutive missed disease assessments and new anticancer therapy, if any
No PD, no death, and no new anticancer treatment	Censored at last disease assessment
No PD and no death, but new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment
<b>Duration of response</b>	<b>Date of progression or censoring</b>
No progression, no death, and no new anticancer therapy is initiated	Censored at last adequate disease assessment
No progression, no death, but new anticancer therapy is initiated	Censored at last adequate disease assessment before new anticancer therapy initiated
Death or progression immediately after $\geq 2$ consecutive missed disease assessments or after new anticancer therapy, if any	Censored at earlier date of last adequate disease assessment prior to $\geq 2$ missed adequate disease assessments and new anticancer therapy, if any
Death or progression after $\leq 1$ missed disease assessment and before new anticancer therapy, if any	Event at date of documented PD or death

8 A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. PD=progressive disease.

9 **Table S3. Number of cycles administered for each component of study treatment in treated participants at the final analysis**

	Pembrolizumab plus gemcitabine and cisplatin (n=529)			Placebo plus gemcitabine and cisplatin (n=534)		
	Pembrolizumab	Gemcitabine	Cisplatin	Placebo	Gemcitabine	Cisplatin
Median (IQR)	9·0 (4·0-15·0)	8·0 (4·0-13·0)	7·0 (4·0-8·0)	8·0 (4·0-14·0)	8·0 (4·0-12·0)	7·0 (4·0-8·0)
≥1	529 (100%)	529 (100%)	527 (<100%)	534 (100%)	534 (100%)	534 (100%)
≥2	490 (93%)	492 (93%)	486 (92%)	498 (93%)	499 (93%)	499 (93%)
≥3	458 (87%)	460 (87%)	450 (85%)	462 (87%)	467 (87%)	464 (87%)
≥4	422 (80%)	426 (81%)	417 (79%)	419 (78%)	420 (79%)	415 (78%)
≥5	388 (73%)	392 (74%)	381 (72%)	377 (71%)	377 (71%)	372 (70%)
≥6	359 (68%)	359 (68%)	346 (65%)	354 (66%)	356 (67%)	347 (65%)
≥7	319 (60%)	315 (60%)	294 (56%)	319 (60%)	313 (59%)	299 (56%)
≥8	302 (57%)	289 (55%)	257 (49%)	297 (56%)	285 (53%)	257 (48%)
≥9	273 (52%)	229 (43%)	1 (<1%)	254 (48%)	209 (39%)	4 (1%)
≥10	248 (47%)	209 (40%)	1 (<1%)	223 (42%)	184 (34%)	2 (<1%)
≥12	206 (39%)	171 (32%)	0	175 (33%)	143 (27%)	0
≥14	156 (29%)	128 (24%)	0	135 (25%)	102 (19%)	0
≥16	129 (24%)	102 (19%)	0	112 (21%)	85 (16%)	0
≥18	101 (19%)	81 (15%)	0	93 (17%)	74 (14%)	0
≥20	84 (16%)	61 (12%)	0	82 (15%)	65 (12%)	0
≥22	69 (13%)	48 (9%)	0	65 (12%)	49 (9%)	0
≥24	64 (12%)	43 (8%)	0	51 (10%)	39 (7%)	0
≥26	55 (10%)	35 (7%)	0	45 (8%)	34 (6%)	0
≥28	41 (8%)	25 (5%)	0	31 (6%)	26 (5%)	0
≥30	35 (7%)	22 (4%)	0	26 (5%)	22 (4%)	0
≥32	28 (5%)	17 (3%)	0	21 (4%)	19 (4%)	0
≥34	24 (5%)	13 (2%)	0	16 (3%)	11 (2%)	0
≥35	20 (4%)	10 (2%)	0	13 (2%)	9 (2%)	0

10

11 **Table S4. Summary of subsequent anticancer therapy in the intention-to-treat population at the final analysis**

	<b>Pembrolizumab plus chemotherapy (n=533)</b>	<b>Placebo plus chemotherapy (n=536)</b>
Any subsequent anticancer therapy*	253 (47%)	261 (49%)
Chemotherapy	230 (43%)	230 (43%)
Immune checkpoint inhibitor	26 (5%)	38 (7%)
Targeted therapy	6 (1%)	18 (3%)
Other	43 (8%)	50 (9%)

12 Data are n (%). \*Participants may have received  $\geq 1$  subsequent anticancer therapy.

13



14 **Table S5. Summary of response in the intention-to-treat population at the final analysis**

	<b>Pembrolizumab plus gemcitabine and cisplatin (n=533)</b>	<b>Placebo plus gemcitabine and cisplatin (n=536)</b>
Objective response rate	156 (29% [25-33])	152 (28% [25-32])
Disease control rate	399 (75 [71-79])	405 (76% [72-79])
Best overall response		
Complete response	14 (3%)	9 (2%)
Partial response	142 (27%)	143 (27%)
Stable disease*	243 (46%)	253 (47%)
Progressive disease	104 (20%)	97 (18%)
Not evaluable†	8 (2%)	11 (2%)
Not assessed‡	22 (4%)	23 (4%)
Time to response, months	2·8 (1·5-4·2)	2·8 (1·5-4·2)
Duration of response,§ months	8·3 (6·9-10·2)	6·8 (5·7-7·1)
Extended duration of response§		
≥3 months	94%	90%
≥6 months	65%	55%
≥9 months	46%	36%
≥12 months	38%	27%
≥15 months	28%	18%
≥18 months	24%	14%
≥21 months	21%	8%
≥24 months	18%	6%

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

19 **Table S6. Treatment-related adverse events that occurred in ≥5% of participants either treatment group in the safety population at the final analysis**

	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	116 (22%)	248 (47%)	121 (23%)	8 (2%)	130 (24%)	255 (48%)	112 (21%)	3 (1%)
Decreased neutrophil count	74 (14%)	158 (30%)	89 (17%)	0	74 (14%)	167 (31%)	79 (15%)	0
Anaemia	155 (29%)	122 (23%)	1 (<1%)	0	138 (26%)	127 (24%)	4 (1%)	0
Decreased platelet count	114 (22%)	55 (10%)	30 (6%)	0	98 (18%)	66 (12%)	33 (6%)	0
Nausea	188 (36%)	7 (1%)	0	0	210 (39%)	9 (2%)	0	0
Fatigue	133 (25%)	20 (4%)	1 (<1%)	0	129 (24%)	18 (3%)	0	0
Decreased white blood cell count	78 (15%)	57 (11%)	4 (1%)	0	78 (15%)	43 (8%)	3 (1%)	0
Decreased appetite	96 (18%)	6 (1%)	1 (<1%)	0	98 (18%)	6 (1%)	0	0
Vomiting	79 (15%)	7 (1%)	0	0	97 (18%)	4 (1%)	0	0
Constipation	84 (16%)	1 (<1%)	0	0	73 (14%)	1 (<1%)	0	0
Rash	70 (13%)	3 (1%)	0	0	35 (7%)	2 (<1%)	0	0
Increased alanine aminotransferase	50 (9%)	6 (1%)	0	0	68 (13%)	3 (1%)	0	0
Pyrexia	53 (10%)	2 (<1%)	0	0	35 (7%)	0	0	0
Alopecia	53 (10%)	0	0	0	65 (12%)	0	0	0
Diarrhoea	48 (9%)	5 (1%)	0	0	52 (10%)	3 (1%)	0	0
Pruritus	52 (10%)	0	0	0	31 (6%)	0	0	0
Asthenia	44 (8%)	7 (1%)	0	0	66 (12%)	15 (3%)	0	0
Hypomagnesaemia	45 (9%)	4 (1%)	0	0	56 (10%)	5 (1%)	0	0
Increased aspartate aminotransferase	41 (8%)	4 (1%)	0	0	51 (10%)	8 (1%)	1 (<1%)	0
Hypothyroidism	40 (8%)	1 (<1%)	0	0	11 (2%)	0	0	0
Increased blood creatinine	38 (7%)	1 (<1%)	0	0	39 (7%)	0	0	0
Peripheral oedema	31 (6%)	0	0	0	28 (5%)	4 (<1%)	0	0
Malaise	29 (5%)	1 (<1%)	0	0	27 (5%)	0	0	0
Dysgeusia	29 (5%)	0	0	0	26 (5%)	1 (<1%)	0	0
Leukopenia	14 (3%)	9 (2%)	2 (<1%)	0	6 (1%)	5 (1%)	1 (<1%)	0
Mucosal inflammation	22 (4%)	2 (<1%)	0	0	22 (4%)	1 (<1%)	0	0
Peripheral sensory neuropathy	22 (4%)	2 (<1%)	0	0	21 (4%)	0	0	0
Decreased lymphocyte count	14 (3%)	5 (1%)	1 (<1%)	0	17 (3%)	9 (2%)	1 (<1%)	0
Stomatitis	16 (3%)	3 (1%)	0	0	25 (5%)	2 (<1%)	0	0

20 Data are n (%).

21

**Table S7. Adverse events that led to death in the as-treated population at the final analysis**

	Pembrolizumab plus gemcitabine and cisplatin group (n=529)			Placebo plus gemcitabine and cisplatin group (n=534)		
	Any cause	Treatment related	Immune mediated	Any cause	Treatment related	Immune mediated
Any death	31 (6%)	8 (2%)	1 (<1%)	49 (9%)	3 (1%)	0
Pneumonia	4 (1%)	0	0	0	0	0
Death	3 (1%)	0	0	5 (1%)	0	0
Sepsis	3 (1%)	0	0	6 (1%)	1 (<1%)	0
Biliary tract infection	2 (<1%)	0	0	0	0	0
Euthanasia	2 (<1%)	0	0	1 (<1%)	0	0
Abdominal abscess	1 (<1%)	1 (<1%)	0	0	0	0
Abdominal infection	1 (<1%)	0	0	0	0	0
COVID-19	1 (<1%)	0	0	4 (1%)	0	0
Cardiac arrest	1 (<1%)	0	0	0	0	0
Cholangitis	1 (<1%)	1 (<1%)	0	0	0	0
Fungal sepsis	1 (<1%)	0	0	0	0	0
Gastrointestinal haemorrhage	1 (<1%)	0	0	0	0	0
Haemorrhagic shock	1 (<1%)	0	0	0	0	0
Lower respiratory tract infection	1 (<1%)	1 (<1%)	0	0	0	0
Malignant neoplasm progression	1 (<1%)	1 (<1%)	0	0	0	0
Myocardial infarction	1 (<1%)	1 (<1%)	0	0	0	0
Pneumocystis jirovecii pneumonia	1 (<1%)	0	0	0	0	0
Pneumonia aspiration	1 (<1%)	0	0	0	0	0
Pneumonia viral	1 (<1%)	1 (<1%)	0	0	0	0
Pneumonitis	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Pulmonary embolism	1 (<1%)	0	0	3 (1%)	0	0
Septic shock	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0
Acute kidney injury	0	0	0	2 (<1%)	0	0
Acute myocardial infection	0	0	0	1 (<1%)	0	0
Biliary sepsis	0	0	0	1 (<1%)	0	0
COVID-19 pneumonia	0	0	0	2 (<1%)	0	0
Cerebral haemorrhage	0	0	0	1 (<1%)	0	0
Cerebral infarction	0	0	0	3 (1%)	0	0
Cerebral venous sinus thrombosis	0	0	0	1 (<1%)	0	0
Cholangitis infective	0	0	0	1 (<1%)	0	0
Cholecystitis	0	0	0	1 (<1%)	0	0
Diarrhoea	0	0	0	1 (<1%)	0	0
Hepatic infection	0	0	0	1 (<1%)	0	0
Hepatorenal syndrome	0	0	0	1 (<1%)	1 (<1%)	0
Ileus	0	0	0	1 (<1%)	0	0
Liver abscess	0	0	0	2 (<1%)	0	0

Lung abscess	0	0	0	1 (<1%)	0	0
Oesophageal varices haemorrhage	0	0	0	1 (<1%)	0	0
Pneumococcal sepsis	0	0	0	1 (<1%)	0	0
Pneumonia acinebacter	0	0	0	1 (<1%)	0	0
Pneumonia bacterial	0	0	0	1 (<1%)	0	0
Post procedural complication	0	0	0	1 (<1%)	0	0
Respiratory failure	0	0	0	1 (<1%)	0	0
Spontaneous bacteria peritonitis	0	0	0	1 (<1%)	0	0
Upper gastrointestinal haemorrhage	0	0	0	2 (<1%)	1 (<1%)	0

23 Data are n (%). Treatment relatedness was determined by the investigator. Potentially immune-mediated adverse events and infusion reactions were based on a  
24 list of terms prepared by the sponsor and were considered regardless of attribution to trial treatment by the investigator; in addition to the specific preferred terms  
25 listed, related terms were included.  
26

27 **Table S8. Potentially immune-mediated adverse events and infusion reactions in the as-treated population at the final analysis**

	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	79 (15%)	35 (7%)	2 (<1%)	1 (<1%)	48 (9%)	18 (3%)	3 (1%)	0
Hypothyroidism	45 (9%)	1 (<1%)	0	0	14 (3%)	0	0	0
Pneumonitis	20 (4%)	5 (1%)	0	1 (<1%)	9 (2%)	0	1 (<1%)	0
Hyperthyroidism	18 (3%)	1 (<1%)	0	0	10 (2%)	0	0	0
Colitis	4 (1%)	4 (1%)	1 (<1%)	0	4 (1%)	2 (<1%)	0	0
Severe skin reactions	0	10 (2%)	0	0	0	3 (1%)	0	0
Hepatitis	4 (1%)	5 (1%)	0	0	0	6 (1%)	1 (<1%)	0
Infusion reactions	6 (1%)	2 (<1%)	0	0	6 (1%)	0	0	0
Pancreatitis	1 (<1%)	3 (1%)	0	0	2 (<1%)	3 (1%)	1 (<1%)	0
Adrenal insufficiency	2 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Thyroiditis	3 (1%)	0	0	0	0	0	0	0
Encephalitis	0	2 (<1%)	0	0	0	0	0	0
Hypophysitis	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Nephritis	2 (<1%)	0	0	0	1 (<1%)	0	0	0
Vasculitis	2 (<1%)	0	0	0	1 (<1%)	0	0	0
Myasthenic syndrome	0	0	1 (<1%)	0	0	1 (<1%)	0	0
Myocarditis	0	0	1 (<1%)	0	0	1 (<1%)	0	0
Myositis	1 (<1%)	0	0	0	0	0	0	0
Hypoparathyroidism	0	0	0	0	1 (<1%)	0	0	0
Uveitis	0	0	0	0	2 (<1%)	0	0	0

28 Data are n (%). Potentially immune-mediated adverse events and infusion reactions were based on a list of terms prepared by the sponsor and were considered  
 29 regardless of attribution to trial treatment by the investigator; in addition to the specific preferred terms listed, related terms were included.  
 30

31 **Table S9. Use of corticosteroids for the treatment of potentially immune-mediated adverse events and infusion reactions in participants in the safety**  
 32 **population who experienced an event at the final analysis**

	Pembrolizumab plus gemcitabine and cisplatin group			Placebo plus gemcitabine and cisplatin group		
	High starting dose*	Low starting dose†	Not treated	High starting dose*	Low starting dose†	Not treated
Adrenal insufficiency	1/3 (33%)	1/3 (33%)	1/3 (33%)	0	1/2 (50%)	1/2 (50%)
Colitis	5/9 (56%)	1/9 (11%)	3/9 (33%)	4/6 (67%)	0	2/6 (33%)
Encephalitis	2/2 (100%)	0	0	0	0	0
Hepatitis	5/9 (57%)	2/9 (22%)	2/9 (22%)	7/7 (100%)	0	0
Hyperthyroidism	1/19 (5%)	0	18/19 (95%)	0	0	10/10 (100%)
Hypoparathyroidism	0	0	0	0	0	1/1 (100%)
Hypophysitis	0	1/2 (50%)	1/2 (50%)	1/2 (50%)	1/2 (50%)	0
Hypothyroidism	1/46 (2%)	0	45/46 (98%)	0	0	14/14 (100%)
Infusion reactions	4/8 (50%)	1/8 (13%)	3/8 (38%)	2/6 (33%)	1/6 (17%)	3/6 (50%)
Myasthenic syndrome	1/1 (100%)	0	0	1/1 (100%)	0	0
Myocarditis	1/1 (100%)	0	0	0	1/1 (100%)	0
Myositis	0	0	1/1 (100%)	0	0	0
Nephritis	1/2 (50%)	1/2 (50%)	0	1/1 (100%)	0	0
Pancreatitis	2/4 (50%)	0	2/4 (50%)	0	0	6/6 (100%)
Pneumonitis	11/26 (42%)	6/26 (23%)	9/26 (35%)	4/10 (40%)	1/10 (10%)	5/10 (50%)
Severe skin reactions	4/10 (40%)	2/10 (20%)	4/10 (40%)	1/3 (33%)	1/3 (33%)	1/3 (33%)
Thyroiditis	0	0	3/3 (100%)	0	0	0
Uveitis	0	0	0	0	0	2/2 (100%)
Vasculitis	0	0	2/2 (100%)	0	0	1/1 (100%)

33 Data are no. of participants treated with corticosteroids/no. of participants with the event (%). \*A high starting dose of corticosteroids was defined as  $\geq 40$  mg/day  
 34 prednisone or equivalent. †A low starting dose of corticosteroids was defined as  $< 40$  mg/day prednisone or equivalent.  
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