Pembrolizumab (biliary carcinoma)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Raphaela Gorris
- Benjamin Becker
- Claudia Kapp
- Petra Kohlepp
- Philip Kranz
- Felix Schwarz
- Claudia Selbach
- Kathrin Wohlhöfner

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Part I: Benefit assessment

I Table of contents

Page

I List of tables I.3
I List of abbreviations I.5
I 1 Executive summary of the benefit assessment I.6
I 2 Research question I.13
I 3 Information retrieval and study pool I.14
I 3.1 Studies included I.14
I 3.2 Study characteristics I.14
I 4 Results on added benefit I.28
I 4.1 Outcomes included I.28
I 4.2 Risk of bias I.31
I 4.3 Results I.32
I 4.4 Subgroups and other effect modifiers I.39
I 5 Probability and extent of added benefit I.40
I 5.1 Assessment of added benefit at outcome level I.40
I 5.2 Overall conclusion on added benefit I.45
I 6 References for English extract I.48

I List of tables[2]

Page

Table 2: Research question of the benefit assessment of pembrolizumab + cisplatin + gemcitabine I.6
Table 3: Pembrolizumab + cisplatin + gemcitabine – probability and extent of added benefit I.12
Table 4: Research question of the benefit assessment of pembrolizumab + cisplatin + gemcitabine I.13
Table 5: Study pool – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. cisplatin + gemcitabine I.14
Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.15
Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine I.17
Table 8: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.21
Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.22
Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.24
Table 11: Information on subsequent oncological therapies (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (KEYNOTE-966 study) I.26
Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.27
Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.29
Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.31
Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabin vs. placebo + cisplatin + gemcitabine I.33
Table 16: Results (side effects) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.36
Table 17: Extent of added benefit at outcome level: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine I.41

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

Table 18: Favourable and unfavourable effects from the assessment of pembrolizumab + cisplatin + gemcitabine vs. cisplatin + gemcitabine I.46
Table 19: Pembrolizumab + cisplatin + gemcitabine – probability and extent of added benefit..... I.47

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AEOSI	Adverse Event of Special Interest
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-BIL21	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cholangiocarcinoma and Gall Bladder specific Module 21
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab (in combination with cisplatin and gemcitabine). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 3 January 2024.

Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with cisplatin and gemcitabine (hereinafter referred to as pembrolizumab + cisplatin + gemcitabine) compared with cisplatin in combination with gemcitabine (hereinafter referred to as cisplatin + gemcitabine) as an appropriate comparator therapy (ACT) for first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of pembrolizumab + cisplatin + gemcitabine

Therapeutic indication	**ACT**[a]
First-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults[b]	Cisplatin + gemcitabine (see Appendix VI to Section K of the Pharmaceutical Directive)[c, d]
a. Presented is the ACT specified by the G-BA. b. Based on the therapy carried out in the intervention arm, it is assumed that, in terms of any comorbidities and their general condition, patients are eligible for intensive combination chemotherapy. c. Necessary measures to eliminate stenoses (especially drainage of the bile ducts) in the study arms remain unaffected. d. Radiotherapy is not part of the ACT; this does not affect its use as an individualized treatment option. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company designated cisplatin + gemcitabine as the ACT, thus following the G-BA's specification.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The KEYNOTE-966 study was included for the benefit assessment of pembrolizumab + cisplatin + gemcitabine.

The KEYNOTE-966 study is an ongoing double-blind RCT comparing pembrolizumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine in the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults. The study included patients who had not yet received any prior therapy for the current disease stage. Patients who had suffered a recurrence more than 6 months after completing neoadjuvant or adjuvant treatment of an earlier disease stage were eligible for inclusion in the study. Patients had to be in general health rated as 0 or 1 on the Eastern Cooperative Oncology Group Performance Status (ECOG-PS). Patients with brain metastases were excluded from the study. Due to these criteria, the KEYNOTE-966 study offers no data on patients with ECOG PS > 1 or with brain metastases.

The KEYNOTE-966 study consists of 2 cohorts: a global cohort and a Chinese extension cohort. A total of 1069 patients were included in the global cohort and assigned to the treatment arms in a 1:1 randomization. The Chinese extension cohort comprises 112 Chinese patients who have already been randomized as part of the global cohort. An additional 46 patients were included in China exclusively for the extension cohort after inclusion of patients in the global cohort had been completed. The Chinese extension cohort therefore consists of 158 patients in total.

Patients in both arms received chemotherapy consisting of cisplatin + gemcitabine in a 3-week cycle on day 1 and day 8. In the intervention arm, pembrolizumab was added on day 1 of the cycle; in the comparator arm, placebo was added. Treatment measures to eliminate stenoses, in particular drainage of the bile ducts, were not restricted in the study. Radiotherapy of symptomatic lesions or the brain was permitted.

In the KEYNOTE-966 study, patients were treated until disease progression or unacceptable toxicity. In addition to these criteria, the duration of treatment with pembrolizumab was limited to a maximum of 35 treatment cycles (approx. 2 years) and that of treatment with cisplatin to a maximum of 8 treatment cycles. In contrast, the duration of treatment with gemcitabine was not restricted in the study beyond the criteria of disease progression and unacceptable toxicity.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

The results of the final data cut-off of 15 December 2022 were used for the present benefit assessment.

Relevance of the cohorts of the KEYNOTE-966 study

The two cohorts of the KEYNOTE-966 study were conducted under an identical study protocol. The 46 patients in the Chinese extension cohort of the KEYNOTE-966 study who are not

already included in the global cohort only account for around 4% of the total study population. It is therefore assumed that not taking into account the 46 additional Chinese patients does not have a relevant impact on the results. Thus, the global cohort is used as a sufficient approximation of the total population of the study for the benefit assessment. Hereinafter, all information on the KEYNOTE-966 study refers to the global cohort of the KEYNOTE-966 study.

Duration of treatment with the study medication

In the KEYNOTE 966 study, treatment with pembrolizumab largely corresponded to the recommendations of the Summary of Product Characteristics (SPC). According to the SPC, treatment with pembrolizumab should only be performed until disease progression or the occurrence of unacceptable toxicity. Notwithstanding, in addition to these termination criteria, in the KEYNOTE-966 study, pembrolizumab treatment was limited to a maximum treatment duration of 35 cycles (approx. 2 years). However, at the final data cut-off, only 13 (2.5%) patients had completed 35 treatment cycles with pembrolizumab, so the deviation in treatment duration specifications between the SPC and the study protocol of the KEYNOTE-966 study is negligible

In the KEYNOTE-966 study, treatment with cisplatin comprised a maximum of 8 cycles. The duration of treatment with gemcitabine in the KEYNOTE 966 study was not restricted beyond the discontinuation criteria of disease progression or unacceptable toxicity. Treatment with cisplatin + gemcitabine should be carried out in accordance with the ACT as specified in the SPCs and in Appendix VI to Section K of the Pharmaceutical Directive (Prescribability of authorized pharmaceuticals for off-label use). While the therapeutic indication of biliary tract carcinoma is not listed in the SPCs for cisplatin and gemcitabine, Annex VI to Section K of the Pharmaceutical Directive states that treatment should be discontinued in the event of tumour progression or unacceptable toxicity, but that the duration of treatment with cisplatin + gemcitabine has been tested for a maximum of 8 cycles or 24 weeks. There is no information on whether treatment with cisplatin + gemcitabine should be discontinued after 8 cycles. The guidelines for the diagnosis and treatment of biliary carcinoma do not specify the treatment duration for cisplatin + gemcitabine. However, it is stated that there is currently insufficient evidence to generally recommend treatment with cisplatin + gemcitabine beyond 8 cycles. In summary, there are currently no general recommendations for the duration of treatment with cisplatin and/or gemcitabine beyond the tested duration of 8 treatment cycles. However, continued treatment is not explicitly excluded. The unrestricted treatment duration with gemcitabine in the KEYNOTE-966 study is therefore of no consequence for the present benefit assessment.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes for the KEYNOTE-966 study is rated as low. The risk of bias of the results for the outcome of overall survival is also rated as low. The risk of bias for the

results of the outcomes “symptoms” (recorded with the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and the EORTC Quality of Life Questionnaire-Cholangiocarcinoma and Gall Bladder specific Module 21 [EORTC QLQ-BIL21]), “health status” (recorded with the visual analogue scale [VAS] of the EQ-5D), and “health-related quality of life” (recorded with the EORTC QLQ-C30 and the EORTC QLQ-BIL21), as well as for the results on the outcomes of serious adverse events (SAEs), severe AEs, immune-related SAEs/severe AEs, and other specific AEs is each rated as high. The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias.

On the basis of the available information, at most an indication, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most hints can be derived for all other outcomes due to the high risk of bias and a limited certainty of results.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. This results in an indication of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

Morbidity

Symptoms (EORTC QLQ-C30)

Appetite loss

For the outcome of appetite loss, a statistically significant difference was found to the disadvantage of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms was no more than marginal. This results in no hint of an added or lesser benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, constipation, and diarrhoea

No statistically significant difference between the treatment groups was shown for any of the outcomes “fatigue”, “nausea and vomiting”, “pain”, “dyspnoea”, “insomnia”, “constipation”, and “diarrhoea”. This results in no hint of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-BIL21)

Tiredness, jaundice, treatment side effects

For each of the outcomes of tiredness, jaundice, treatment side effects, a statistically significant difference was found to the disadvantage of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. However, the extent of the effect for these outcomes in the category of non-serious/non-severe symptoms was no more than marginal. This results in no hint of an added or lesser benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine in each case; an added benefit is therefore not proven in each case.

Pain, eating, drains

No statistically significant difference between the treatment groups was shown for any of the outcomes of pain, eating, or drains. This results in no hint of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

Health status

There was no statistically significant difference between treatment groups for the outcome of health status. This results in no hint of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BIL21

No statistically significant difference between treatment groups was found for any of the health-related quality of life outcomes. This results in no hint of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuations due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. In each case, this results in no hint of greater or lesser harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; greater or lesser harm is therefore not proven.

immune-related severe AEs

For the outcome of immune-related severe AEs, a statistically significant difference was found to the disadvantage of pembrolizumab + cisplatin + gemcitabine in comparison with placebo +

cisplatin + gemcitabine. This resulted in a hint of greater harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

immune-related SAEs

No statistically significant difference between the treatment groups was shown for the outcome "immune-related SAEs". This results in no hint of greater or lesser harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; greater or lesser harm is therefore not proven.

Specific AEs

Rash (AEs), cardiac disorders (SAEs), fever (SAEs), neutrophil count decreased (SAEs)

For each of the outcomes of rash (AEs), cardiac disorders (SAEs), fever (SAEs), and neutrophil count decreased (SAEs) a statistically significant difference was found to the disadvantage of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. In each case, this resulted in a hint of greater harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

Liver abscess (severe AEs)

For the outcome of liver abscess (severe AEs), a statistically significant difference was found in favour of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. This resulted in a hint of lesser harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the extent and probability of the added benefit of the drug pembrolizumab compared with the ACT is assessed as follows:

In summary, both favourable and unfavourable effects of pembrolizumab + cisplatin + gemcitabine were found in comparison with cisplatin + gemcitabine. Only for overall survival are the observed effects based on the entire observation period. For morbidity, health-related

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

quality of life and side effects, in contrast, they are based exclusively on the shortened period (up to 30 or 90 days after the last dose of study medication).

For the favourable effects, there was an indication of minor added benefit for the outcome of overall survival. Furthermore, a hint of lesser harm of minor extent was found for the outcome of liver abscess (severe AEs). On the side of unfavourable effects, there is a hint of lesser harm for immune-related severe AEs and for the specific AEs of cardiac disorders (SAE), fever (SAE), neutrophil count decreased (SAE) and rash (AE) each a hint of considerable harm Overall, the unfavourable effects do not call into question the added benefit in the outcome of overall survival.

In summary, there is an indication of a minor added benefit from pembrolizumab + cisplatin + gemcitabine in comparison with the ACT cisplatin + gemcitabine for adults with locally advanced unresectable or metastatic biliary tract carcinoma in first-line treatment.

Table 3 shows a summary of the probability and extent of added benefit of pembrolizumab + cisplatin + gemcitabine.

Table 3: Pembrolizumab + cisplatin + gemcitabine – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults[b, c]	Cisplatin + gemcitabine (see Appendix VI to Section K of the Pharmaceutical Directive)[d, e]	Indication of minor added benefit

a. Presented is the ACT specified by the G-BA.
b. Only patients with an ECOG PS of 0 or 1 were included in the KEYNOTE-966 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.
c. Based on the therapy carried out in the intervention arm, it is assumed that, in terms of any comorbidities and their general condition, patients are eligible for intensive combination chemotherapy.
d. Necessary measures to eliminate stenoses (especially drainage of the bile ducts) in the study arms remain unaffected.
e. Radiotherapy is not part of the ACT; this does not affect its use as an individualized treatment option.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with cisplatin and gemcitabine (hereinafter referred to as pembrolizumab + cisplatin + gemcitabine) compared with cisplatin in combination with gemcitabine (hereinafter referred to as cisplatin + gemcitabine) as an ACT for first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pembrolizumab + cisplatin + gemcitabine

Therapeutic indication	**ACT**[a]
First-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults[b]	Cisplatin + gemcitabine (see Appendix VI to Section K of the Pharmaceutical Directive)[c, d]
a. Presented is the ACT specified by the G-BA. b. Based on the therapy carried out in the intervention arm, it is assumed that, in terms of any comorbidities and their general condition, patients are eligible for intensive combination chemotherapy. c. Necessary measures to eliminate stenoses (especially drainage of the bile ducts) in the study arms remain unaffected. d. Radiotherapy is not part of the ACT; this does not affect its use as an individualized treatment option. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company designated cisplatin + gemcitabine as the ACT, thus following the G-BA's specification.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on pembrolizumab (status: 2 November 2023)
- bibliographical literature search on pembrolizumab (last search on 2 November 2023)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 13 November 2023)
- search on the G-BA website for pembrolizumab (last search on 13 November 2023)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 15 January 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. cisplatin + gemcitabine

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
KEYNOTE-966	Yes	Yes	No	Yes [3,4]	Yes [5-7]	Yes [8]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that selected by the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE-966	RCT, double-blind, parallel	▪ Adults (≥ 18 years) with metastatic and/or unresectable biliary tract carcinoma[b] without prior therapy for the current disease stage or with a recurrence (≥ 6 months) after neoadjuvant/adjuvant therapy[c] ▪ ECOG PS ≤ 1	Global cohort: ▪ Pembrolizumab + cisplatin + gemcitabine (N = 533) ▪ Placebo + cisplatin + gemcitabine (N = 536) ▪ Chinese extension cohort[d]: ▪ Pembrolizumab + cisplatin + gemcitabine (N = 75) ▪ Placebo + cisplatin + gemcitabine (N = 83)	▪ Screening: up to 28 days ▪ Treatment: Pembrolizumab: until disease progression or unacceptable toxicity, for a maximum of 35 cycles[e] (approx. 2 years) Cisplatin: for a maximum of 8 cycles Gemcitabine: until disease progression or unacceptable toxicity[e] ▪ Observation[f]: outcome-specific, at most until either death, discontinuation of participation in the study, or end of study	185 centres in Argentina, Australia, Belgium, Brazil, Canada, Chile, China, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Malaysia, Netherlands, New Zealand, Spain, South Korea, Taiwan, Thailand, Turkey, United Kingdom, United States 09/2019–ongoing Data cut-offs for global cohort: ▪ Interim analysis I[g]: 15 Dec 2021 ▪ Interim analysis II[g]: 25 May 2022 ▪ Final analysis[h]: 15 Dec 2022 ▪ Safety update[i]: 13 Apr 2023	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Intra- or extrahepatic or gallbladder carcinoma; patients with ampullary carcinoma were excluded from the study.
c. Without gemcitabine and/or cisplatin.
d. In addition to 112 Chinese patients included in the global cohort, the Chinese extension cohort includes 46 additional patients who were randomized in China after completion of the randomization of the global cohort in order to meet Chinese regulatory requirements. The benefit assessment is based on the results of the global cohort (see Section I 3.2); the Chinese extension cohort is no longer shown in the following tables.
e. Patients who achieved a confirmed complete response according to RECIST 1.1 after at least 8 cycles of treatment with pembrolizumab and received at least 2 further cycles of treatment with pembrolizumab after complete response were allowed to interrupt the study treatment. In the event of subsequent confirmed disease progression, treatment with pembrolizumab could be continued for up to 17 further cycles ("second course phase"). The decision to continue treatment with gemcitabine during the "second course phase" was at the discretion of the investigator.
Moreover, patients with stable disease, complete or partial response after completion of the full of treatment with pembrolizumab over 35 cycles were also allowed to start treatment with up to 17 further cycles of pembrolizumab in the event of subsequent confirmed disease progression, if they had not received any other subsequent therapy by then. The decision to continue treatment with gemcitabine during the "second course phase" was at the discretion of the investigator.
At the final data cut-off, 2 patients had started a retreatment during the "second course phase", but discontinued it due to disease progression.
f. Outcome-specific information is provided in Table 8.
g. Prespecified interim analyses after approx. 585 deaths and 26 months or 695 deaths and 32 months.
h. Prespecified after approx. 818 deaths and 38 months.
i. Non-prespecified data cut-off as part of regular safety updates.

AE: adverse event; CSR: clinical study report; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; RECIST: Response Evaluation Criteria in Solid Tumours; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (multipage table)

Study	Intervention	Comparison
KEYNOTE-966	3-week cycles with ▪ pembrolizumab 200 mg IV on day 1 of a 3-week cycle ▪ + ▪ cisplatin 25 mg/m² BSA IV on day 1 and day 8 (for a maximum of 8 cycles) ▪ + ▪ gemcitabine 1000 mg/m² BSA IV on day 1 and day 8	3-week cycles with ▪ placebo IV on day 1 (for a maximum of 35 cycles) ▪ + ▪ cisplatin 25 mg/m² BSA IV on day 1 and day 8 (for a maximum of 8 cycles) ▪ + ▪ gemcitabine 1000 mg/m² BSA IV on day 1 and day 8
	Treatment adjustment ▪ Each new cycle could [be] delayed to ensure recovery between treatment cycles. ▪ Dose reductions[a] ▫ Pembrolizumab or placebo: disallowed ▫ Cisplatin or gemcitabine: according to the SPC ▪ Treatment interruption due to toxicity[a] ▫ Pembrolizumab or placebo: for up to 12 weeks after the last dose ▫ Cisplatin or gemcitabine: for up to 6 weeks after the last dose	
	Disallowed pretreatment ▪ Treatment with an anti-PD-1, anti-PD-L1 or anti-PD-L2 drug or a drug against another stimulating or co-inhibiting T-cell receptor ▪ Systemic cancer therapy including investigational products against the current disease stage within 4 weeks prior to the start of study treatment Radiotherapy within 2 weeks prior to the start of study treatment **Allowed concomitant treatment** ▪ Any treatment at the discretion of the investigator according to local standards that is necessary for the patients' wellbeing. **Disallowed concomitant treatment** ▪ Antineoplastic systemic chemotherapy or biological therapy ▪ Immunotherapy or chemotherapy other than the defined study therapy ▪ any drugs that are disallowed according to the SPC for combination with cisplatin and gemcitabine ▪ Radiotherapy[b] ▪ Live vaccines ≤ 30 days before the first study medication and during the study ▪ Permanent immunosuppressive therapy except for the treatment of side effects of immunological origin[c]	

a. Where the investigator clearly determined the specific component causing toxicity, it was possible to interrupt, reduce (except pembrolizumab), or discontinue any drug of the combination therapy independently from the other drugs.
b. Radiotherapy of symptomatic lesions or the brain was allowed at the physician's discretion.
c. Systemic glucocorticoids were allowed for the following use: treatment of symptoms of immunological origin, prophylaxis of vomiting or contrast medium allergies, short-term use (at doses > 10 mg/day prednisone equivalent) for chronic obstructive pulmonary disease, permanent systemic replacement therapy (≤ 10 mg/day prednisone equivalent) as well as topical, ocular, intra-articular and inhalation application.

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (multipage table)

Study	Intervention	Comparison
BSA: body surface area; IV: intravenous; PD: programmed cell death; PD-L1/2: programmed cell death ligand 1/2; RCT: randomized controlled trial; SPC: Summary of Product Characteristics		

The KEYNOTE-966 study is an ongoing double-blind RCT comparing pembrolizumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine in the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults. The study included patients who had not yet received any prior therapy for the current disease stage. Patients who had suffered a recurrence more than 6 months after completing neoadjuvant or adjuvant treatment of an earlier disease stage were eligible for inclusion in the study. Patients had to be in general health rated as 0 or 1 on the Eastern Cooperative Oncology Group Performance Status (ECOG-PS). Patients with brain metastases were excluded from the study. Due to these criteria, the KEYNOTE-966 study offers no data on patients with ECOG PS > 1 or with brain metastases.

The KEYNOTE-966 study consists of 2 cohorts: a global cohort and a Chinese extension cohort. A total of 1069 patients were included in the global cohort of the study and were randomly assigned to the treatment arms in a 1:1 ratio. 533 patients were assigned to the intervention arm, 536 patients to the comparator arm. Randomization was stratified by region (Asia or non-Asia), disease status (locally advanced or metastatic) and site of origin (extrahepatic, gallbladder or intrahepatic). The Chinese extension cohort comprises 112 Chinese patients who have already been randomized as part of the global cohort. An additional 46 patients were included in China exclusively for the Chinese extension cohort after inclusion of patients in the global cohort had been completed in order to fulfil the requirements of the Chinese regulatory authorities. Therefore, the Chinese extension cohort consists of a total of 158 patients, 75 patients in the intervention arm and 83 patients in the comparator arm.

Patients in both arms received chemotherapy consisting of cisplatin + gemcitabine in a 3-week cycle on day 1 and day 8. In the intervention arm, pembrolizumab was added on day 1 of the cycle; in the comparator arm, placebo was added. Treatment measures to eliminate stenoses, in particular drainage of the bile ducts, were not restricted in the study. Radiotherapy of symptomatic lesions or the brain was permitted.

In the KEYNOTE-966 study, patients were treated until disease progression or unacceptable toxicity. In addition to these criteria, the duration of treatment with pembrolizumab [9] was limited to a maximum of 35 treatment cycles (approx. 2 years) and that of treatment with cisplatin to a maximum of 8 treatment cycles. In contrast, the duration of treatment with gemcitabine was not restricted in the study beyond the criteria of disease progression and

unacceptable toxicity. The deviations of the specifications for the treatment duration of the KEYNOTE-966 study from the information of the respective SPCs [9-11] and from Appendix VI to Section K of the Pharmaceutical Directive (Prescribability of authorized pharmaceuticals for off-label use [12]) are discussed below.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Relevance of the cohorts of the KEYNOTE-966 study

The company exclusively used the data of the global cohort of the KEYNOTE-966 study for its benefit assessment. It did not consider the results of the Chinese extension cohort and justified this with the comparatively small patient population compared to the global cohort of the study and the questionable transferability of the results to the German health care context. Furthermore, it pointed out that the results of the Chinese extension cohort are consistently consistent with those of the global cohort and that including them in the derivation of an added benefit would have no influence. The company did not present the data of the Chinese extension cohort separately in Module 4 A, but submitted a corresponding CSR for the final data cut-off on 15 December 2022.

The two cohorts of the KEYNOTE-966 study were conducted under an identical study protocol. The only exception was a separate statistical analysis plan for the Chinese extension cohort. Thus, both cohorts should be considered as 1 study and the results for the entire study population should generally be used as the basis for the benefit assessment. The 46 patients in the Chinese extension cohort of the KEYNOTE-966 study who are not already included in the global cohort only account for around 4% of the total study population, however. It is therefore assumed that not taking into account the 46 additional Chinese patients does not have a relevant impact on the results. Thus, the global cohort is used as a sufficient approximation of the total population of the study for the benefit assessment. Hereinafter, all information on the KEYNOTE-966 study refers to the global cohort of the KEYNOTE-966 study.

Duration of treatment with the study medication

In the KEYNOTE-966 study, treatment with pembrolizumab largely corresponded to the recommendations of the SPC [9]. According to the SPC, treatment with pembrolizumab should only be performed until disease progression or the occurrence of unacceptable toxicity. Notwithstanding, in addition to these termination criteria, in the KEYNOTE-966 study, pembrolizumab treatment was limited to a maximum treatment duration of 35 cycles (approx. 2 years). However, at the final data cut-off, only 13 (2.5%) patients had completed 35 treatment cycles with pembrolizumab, so the deviation in treatment duration specifications between the SPC and the study protocol of the KEYNOTE-966 study is negligible

In the KEYNOTE-966 study, treatment with cisplatin comprised a maximum of 8 cycles. The duration of treatment with gemcitabine in the KEYNOTE966 study was not restricted beyond the discontinuation criteria of disease progression or unacceptable toxicity. 229 (43.3%) patients in the intervention arm and 209 (39.1%) patients in the comparator arm were treated with gemcitabine for more than 8 cycles. For 5 (0.9%) patients in the intervention arm and 3 (0.6%) patients in the comparator arm, treatment with gemcitabine was continued beyond the 35 treatment cycles with pembrolizumab.

Treatment with cisplatin + gemcitabine should be carried out in accordance with the ACT as specified in the SPCs [10,11] and in Appendix VI to Section K of the Pharmaceutical Directive (Prescribability of authorized pharmaceuticals for off-label use [12]). While the therapeutic indication of biliary tract carcinoma is not listed in the SPCs for cisplatin and gemcitabine, Annex VI to Section K of the Pharmaceutical Directive states that treatment should be discontinued in the event of tumour progression or unacceptable toxicity, but that the duration of treatment with cisplatin + gemcitabine has been tested for a maximum of 8 cycles or 24 weeks. There is no information on whether treatment with cisplatin + gemcitabine should be discontinued after 8 cycles. The guidelines for the diagnosis and treatment of biliary carcinoma [13,14] do not specify the treatment duration for cisplatin + gemcitabine. However, it is stated that there is currently insufficient evidence to generally recommend treatment with cisplatin + gemcitabine beyond 8 cycles [14]. The decision on continued treatment should be made individually for each patient, taking into account the effectiveness and tolerability [14].

In summary, there are currently no general recommendations for the duration of treatment with cisplatin and/or gemcitabine beyond the tested duration of 8 treatment cycles. However, continued treatment is not explicitly excluded. The unrestricted treatment duration with gemcitabine in the KEYNOTE-966 study is therefore of no consequence for the present benefit assessment.

Data cut-offs

The KEYNOTE-966 study protocol provided for the following data cut-offs:

- Data cut-off from 15 December 2021: interim analysis to collect efficacy and safety data after approx. 585 deaths and 26 months
- Data cut-off from 25 May 2022: interim analysis to collect efficacy and safety data after 695 deaths and 32 months
- Data cut-off from 15 December 2022: final analysis of all outcomes on mortality, morbidity, health-related quality of life and side effects after the occurrence of approx. 818 deaths and about 38 months after the start of randomization.

As both interim analyses showed no superiority in the primary outcome of overall survival, no unblinding was performed and no further outcomes were analysed. There are no analyses available in the dossier for these two data cut-offs. In the present benefit assessment, the results presented by the company for all outcomes at the final data cut-off of the KEYNOTE-966 study are evaluated.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE-966	
Mortality	
Overall survival	▪ Until death, withdrawal of consent, or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-BIL21)	▪ Up to 30 days after the last dose of the study medication
Health status (EQ-5D VAS)	
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-BIL21	▪ Up to 30 days after the last dose of the study medication
Side effects	
AEs/severe AEs[a]	▪ Up to 30 days after the last dose of the study medication
SAEs	▪ Up to 90 days after the last dose of the study medication or up to 30 days after the last dose of the study medication when starting subsequent therapy

a. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BIL21: Quality of Life Questionnaire-Cholangiocarcinoma and Gall Bladder specific Module 21; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 or 90 days). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study Characteristic Category	**Pembrolizumab + cisplatin + gemcitabine N[a] = 533**	**Placebo + cisplatin + gemcitabine N[a] = 536**
KEYNOTE-966		
Age [years], mean (SD)	63 (10)	62 (11)
Sex [F/M], %	47/53	49/51
Region (by stratification factor)[b], n (%)		
Asia	242 (45)	244 (45)
Non-Asia	291 (55)	292 (55)
Region[c], n (%)		
North America	45 (8)	40 (8)
Rest of the world	337 (63)	345 (64)
Western Europe	151 (28)	151 (28)
ECOG PS, n (%)		
0	258 (48)	228 (43)
1	274 (51)	308 (58)
≥ 2	1 (< 1)	0 (0)
Prior surgery, n (%)		
Yes	157 (29)	162 (30)
No	376 (71)	374 (70)
Prior chemotherapy, n (%)		
Yes	50 (9)	48 (9)
No	483 (91)	488 (91)
PD-L1 status (CPS ≥ 1), n (%)		
CPS ≥ 1	363 (68)	365 (68)
CPS < 1	113 (21)	110 (21)
Indeterminable	57 (11)	61 (11)
MSI status, n (%)		
MSI-H	6 (1)	4 (< 1)
MSS	433 (81)	422 (79)
Indeterminable	94 (18)	110 (21)
Disease status, n (%)		
Locally advanced	60 (11)	66 (12)
Metastatic	473 (89)	470 (88)
Site of origin, n (%)		
Extrahepatic	98 (18)	105 (20)
Gallbladder	115 (22)	118 (22)
Intrahepatic	320 (60)	313 (58)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study Characteristic Category	Pembrolizumab + cisplatin + gemcitabine N[a] = 533	Placebo + cisplatin + gemcitabine N[a] = 536
Treatment discontinuation, n (%)[b]	489 (92)	504 (94)
Study discontinuation, n (%)[c]	414 (78)	446 (83)

a. Number of randomized patients.
b. Common reasons for treatment discontinuation in the intervention arm versus control arm were: disease progression as per RECIST 1.1 (61.2% vs. 66.3%), AEs (12.7% vs. 11.4%), clinical progression (6,6% vs. 8,1%), and investigator's decision (6.0% vs. 3.0 %).
c. The most common reason for study discontinuation in the intervention arm versus control arm was patient death (76.7% versus 82.6%).

AE: adverse event; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; f: female; m: male; MSI: microsatellite instability; MSI-H: microsatellite instability-high; MSS: microsatellite stability; n: number of patients in the category; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RECIST: Response Evaluation Criteria in Solid Tumors; RCT: randomized controlled trial; RECIST: Response-Evaluation-Criteria-In-Solid-Tumors; SD: standard deviation

The patient characteristics of the KEYNOTE-966 study are largely comparable between the 2 treatment arms. The mean age of the patients was 63 years in the intervention arm and 62 years in the comparator arm; slightly more than half of the patients in both arms came from non-Asian regions. Most patients had metastatic carcinoma (89 versus 88 %). The site of origin was within the liver in more than half of the patients, in the gallbladder in 22% of the patients and outside the liver in 18% of the patients in the intervention arm and 20% of the patients in the comparator arm. The proportion of patients with prior chemotherapy was less than 10% in both arms.

Table 10 shows the mean and median treatment durations of the patients and the mean and median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + cisplatin + gemcitabine**	**Placebo + cisplatin + gemcitabine**
KEYNOTE-966		
Treatment duration[a] [months]	N = 529	N = 534
Median [Q1; Q3]	6.4 [2.8; 10.8]	5.5 [2.5; 9.7]
Mean (SD)	8.0 (6.9)	7.3 (6.3)
Observation period [months]		
Overall survival[b,c]	N = 533	N = 536
Median [Q1; Q3]	12.7 [6.8; 20.3]	10.8 [5.7; 18.6]
Mean (SD)	14.0 (8.6)	12.7 (8.4)
Morbidity		
EORTC QLQ-C30, EQ-5D VAS[d]	N = 520	N = 517
Median [Q1; Q3]	7.0 [3.3; 11.3]	6.1 [3.0; 10.2]
Mean (SD)	7.8 (5.8)	7.3 (5.6)
EORTC QLQ-BIL21[d]	N = 520	N = 516
Median [Q1; Q3]	7.0 [3.3; 11.3]	6.1 [3.0; 10.2]
Mean (SD)	7.8 (5.8)	7.4 (5.6)
Health-related quality of life		
EORTC QLQ-C30[d]	N = 520	N = 517
Median [Q1; Q3]	7.0 [3.3; 11.3]	6.1 [3.0; 10.2]
Mean (SD)	7.8 (5.8)	7.3 (5.6)
EORTC QLQ-BIL21[d]	N = 520	N = 516
Median [Q1; Q3]	7.0 [3.3; 11.3]	6.1 [3.0; 10.2]
Mean (SD)	7.8 (5.8)	7.4 (5.6)
Side effects[e]		
AEs, severe AEs[f]	N = 529	N = 534
Median [Q1; Q3]	7.4 [3.8; 11.8]	6.5 [3.4; 10.7]
Mean (SD)	9.0 (6.9)	8.2 (6.3)
SAEs	N = 529	N = 534
Median [Q1; Q3]	8.7 [5.3; 13.6]	8.3 [4.8; 12.4]
Mean (SD)	10.4 (6.9)	9.6 (6.4)

a. Calculated from the date of the first dose of any study medication to the date of the last dose of any study medication; data refer to patients who have received at least 1 dose of study medication.
b. The observation period was calculated based on the observed time to event/censoring/final data cut-off of all patients (deceased and non-deceased).
c. Data refer to all randomised patients.
d. Data refer to all randomised patients who received at least 1 dose of the study medication and for whom at least 1 survey of patient-reported outcomes was available.
e. Data refer to patients who received at least one 1 dose of study medication.
f. Severe AEs are operationalized as CTCAE grade ≥ 3.

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + cisplatin + gemcitabine**	**Placebo + cisplatin + gemcitabine**
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; N: number of analysed patients of the respective population; Q1: 1st quartile; Q3: 3rd quartile; QLQ-BIL21: Quality of Life Questionnaire-Cholangiocarcinoma and Gall Bladder specific Module 21; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale		

In the KEYNOTE-966 study, the median treatment duration is similar in both treatment arms, being about 1 month longer in the intervention arm than in the comparator arm (6.4 months versus 5.5 months).

The median observation period for the outcome of overall survival is 12.7 months in the intervention arm, slightly longer than 10.8 months in the comparator arm.

The observation periods for the outcomes on symptoms, health-related quality of life and side effects were linked to the end of treatment in each case (see Table 8) and are up to 1 month longer in the intervention arm than in the comparator arm, at a median of 7 months and 8.7 months for serious adverse events (SAEs) respectively. The observation periods are therefore comparable overall. Compared to overall survival, data for these outcomes are only available for a shorter observation period.

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent oncological therapies (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (KEYNOTE-966 study)

Study **Drug class** **Drug**[a]	**Patients with subsequent therapy, n (%)**	
	Pembrolizumab + cisplatin + gemcitabine **N = 533**	**Placebo + cisplatin + gemcitabine** **N = 536**
KEYNOTE-966		
Total	253 (47.5)	261 (48.7)
Chemotherapy	230 (43.2)	230 (42.9)
Capecitabine	49 (9.2)	51 (9.5)
Carboplatin	6 (1.1)	4 (0.7)
Cisplatin	50 (9.4)	56 (10.4)
Fluorouracil	126 (23.6)	127 (23.7)
Gemcitabine	41 (7.7)	42 (7.8)
Gemcitabine hydrochloride	9 (1.7)	8 (1.5)
Gimeracil/oteracil potassium/tegafur	37 (6.9)	33 (6.2)
Irinotecan	45 (8.4)	42 (7.8)
Irinotecan hydrochloride	8 (1.5)	12 (2.2)
Oxaliplatin	109 (20.5)	111 (20.7)
Paclitaxel	7 (1.3)	5 (0.9)
Nab-paclitaxel	14 (2.6)	15 (2.8)
Immune checkpoint inhibitors	26 (4.9)	38 (7.1)
Nivolumab	8 (1.5)	18 (3.4)
Targeted therapy	6 (1.1)	18 (3.4)
Pemigatinib	2 (0.4)	8 (1.5)
Other	43 (8.1)	50 (9.3)
Lenvatinib	5 (0.9)	8 (1.5)
Lenvatinib mesylate	7 (1.3)	4 (0.7)

a. Patients are only counted once in the drug class of the systemic therapy in which a subsequent therapy has occurred.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In the KEYNOTE-966 study, switching from the comparator arm to the intervention arm after disease progression was disallowed according to the study protocol. Furthermore, subsequent therapy was allowed without restrictions in both study arms. In both study arms, slightly less than half of the patients received a subsequent therapy. Patients most frequently received chemotherapy as a subsequent therapy, with fluorouracil, oxaliplatin, cisplatin, capecitabine and irinotecan being the most used drugs. The proportions were comparable between the

treatment arms. Patients in the comparator arm were more likely to receive an immune checkpoint inhibitor (7.1%) than patients in the intervention arm (4.9%). Patients in both treatment arms only rarely received targeted therapy (1.1% vs. 3.4%).

Overall, the therapies administered following the treatment in the KEYNOTE-966 study largely correspond to the treatment options outlined in the S3 guideline [13]. Following failure of first-line treatment in patients with good general health, these consist of a treatment regimen with oxaliplatin or irinotecan or of targeted therapy if corresponding molecular genetic markers are present.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE-966	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the KEYNOTE-966 study is rated as low.

Transferability of the study results to the German health care context

According to the company, the results of the KEYNOTE-966 study are fully transferable to the German health care context. The company bases this on the characteristics of the analysed patient population, the study design and the approval-compliant use of pembrolizumab + cisplatin + gemcitabine.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms, recorded using the EORTC QLQ-C30 and EORTC QLQ-BIL21
  - Health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - Recorded using the EORTC QLQ-C30 and the EORTC QLQ-BIL21
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Immune-related SAEs
  - Immune-related severe AEs (CTCAE grade ≥ 3)
  - Other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30 and EORTC QLQ-BIL21)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BIL21)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs[b]	Immune-related severe AEs[a,b]	Other specific AEs[c]
KEYNOTE-966	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The operationalization of a specific MedDRA PT collection from the AEOSI outcome presented by the company is used in each case.
c. The following events are considered (MedDRA-coded): rash (PT, AEs), cardiac disorders (SOC, SAEs), fever (PT, SAEs), neutrophil count decreased (PT, SAEs), and liver abscess (PT, severe AEs).

AE: adverse event; AEOSI: adverse events of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BIL21: Quality of Life Questionnaire-Cholangiocarcinoma and Gall Bladder specific Module 21; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on the included outcomes and analyses

Morbidity and health-related quality of life

Health status

Health status was surveyed by EQ-5D VAS. In the study, the observation of the mean value differences from the start of the study to the last observation time was prespecified. In Module 4 A, the company presented a responder analysis on the time to first deterioration by ≥ 15 points (scale range 0 to 100). This was used for the present benefit assessment.

EORTC QLQ-C30 and EORTC QLQ-BIL21

In Module 4 A, the company presented responder analyses for the outcomes of morbidity and health-related quality of life, assessed with the EORTC QLQ-C30 and the disease-related module EORTC QLQ-BIL21, on the time to first deterioration by ≥ 10 points per scale (respective scale range 0 to 100). The company conducted these analyses post-hoc for Module 4 A of the dossier.

In the KEYNOTE-966 study, responder analyses for the scales on global health status, physical function, pain, and jaundice were prespecified for the time to confirmed deterioration by ≥ 10 points. A deterioration was considered confirmed if the response criterion of deterioration by ≥ 10 points was achieved in 2 consecutive surveys. In the KEYNOTE-966 study, there were no relevant differences in observation periods between the treatment arms in the outcome categories “morbidity” and “health-related quality of life” (see Section I 3.2, Table 10). Therefore, responder analyses for permanent deterioration would potentially be possible. The responder analyses on time to confirmed deterioration by ≥ 10 points planned in the study are also basically sensible in terms of content [1]. However, as these analyses are only available in the CSR for individual scales of the two instruments, the responder analyses presented in Module 4 A for all scales regarding time to first deterioration by ≥ 10 points are used for the benefit assessment.

Outcome category of the EORTC QLQ-BIL21

In the morbidity category, the company presented results on the EORTC QLQ-BIL21. The EORTC QLQ-BIL21 is a disease-specific additional module to the EORTC QLQ-C30 for patients with biliary tract and gallbladder cancer and comprises 21 items. The 21 items are assigned to the 5 scales of eating (3 items), jaundice (3 items), tiredness (3 items), pain (4 items), and anxiety (4 items). The scales of treatment side effects, drains, and weight loss are each 1-item scales. Like the company, this assessment assigned the scales of eating, jaundice, tiredness, pain, and drains to the outcome category of symptoms. Unlike the company, it assigned the scales of anxiety and weight loss to the health-related quality of life category.

Side effects

In the analysis of side effects, the number of patients in whom an event occurred is primarily relevant. However, when analysing the time until occurrence of the events, effects may also result from an earlier or later occurrence of the event rather than on the basis of the proportions. Time-to-event analyses are of particular relevance in between-group comparisons with different mean observation periods [1]. The company presented time-to-event analyses for all side effects outcomes. In the present situation, however, the mean observation periods between the treatment arms are sufficiently similar (see Table 10) to use the relative risk as an effect measure to derive the added benefit for all outcomes in the side effects category.

For the side effects, the company stated that the MedDRA-coded terms "neoplasm progression", "malignant neoplasm progression", and "disease progression"were not considered as disease-related events in its analyses. This approach is adequate to exclude events representing progression of the underlying disease from the analyses. Nevertheless, the analyses of the company on the outcome "discontinuation due to AEs" include one event for "malignant neoplasm progression" in the intervention arm (see Table 23 in I Appendix C of

the full dossier assessment). Due to the negligible proportion (< 1%), this is of no consequence for the benefit assessment.

Immune-related SAEs and immune-related severe AEs

For the outcomes of immune-related SAEs and immune-related severe AEs (defined in the KEYNOTE-966 study as AEOSIs), the predefined list of preferred terms (PTs), which was presented by the company, is deemed a suitable operationalization and is used in the present benefit assessment.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

Study		Outcomes									
	Study level	Overall survival	Symptoms (EORTC QLQ-C30 and EORTC QLQ-BIL21)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BIL21)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs[b]	Immune-related severe AEs[a,b]	Other specific AEs[c]
KEYNOTE-966	L	L	H[d]	H[d]	H[d]	H[d]	H[d]	L[e]	H[d]	H[d]	H[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") presented by the company is used.
c. The following events are considered (MedDRA-coded): rash (PT, AEs), cardiac disorders (SOC, SAEs), fever (PT, SAEs), neutrophil count decreased (PT, SAEs), and liver abscess (PT, severe AEs).
d. Incomplete observations for potentially informative reasons.
e. Despite low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be limited (see body of text below).

AE: adverse event; AEOSI: adverse events of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BIL21: Quality of Life Questionnaire-Cholangiocarcinoma and Gall Bladder specific Module 21; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

For the results on the outcome of overall survival, the risk of bias is rated as low.

The outcome-specific risk of bias for the results of the outcomes “symptoms” (EORTC QLQ-C30 and EORTC QLQ-BIL21), “health status” (EQ-5D VAS), “health-related quality of life” (EORTC QLQ-C30 and EORTC QLQ-BIL21), as well as for the side effect outcomes SAEs, Severe AEs, immune-related SAEs/severe AEs and other specific AEs is rated as high. This is due to incomplete observations for potentially informative reasons, as these outcomes were only followed up for 30 and 90 days after the last dose of study medication.

The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Despite a low risk of bias of the results, the certainty of results is reduced for the outcome of discontinuation due to AEs. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after treatment discontinuation for other reasons, AEs which would have led to discontinuation may have occurred, but the criterion of discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

I 4.3 Results

Table 15 and Table 16 summarize the results comparing pembrolizumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine in adults with locally advanced unresectable or metastatic biliary tract carcinoma in first-line treatment. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier.

Kaplan-Meier curves on the presented event time analyses can be found in I Appendix B of the full dossier assessment. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment. A list of the occurred categories of immune-related AEs, immune-related SAEs and immune-related severe AEs is provided as supplementary information in I Appendix D of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabin vs. placebo + cisplatin + gemcitabine (multipage table)

Study Outcome category Outcome	Pembrolizumab + cisplatin + gemcitabine		Placebo + cisplatin + gemcitabine		Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
KEYNOTE-966					
Mortality					
Overall survival	533	12.7 [11.5; 13.6] 414 (77.7)	536	10.9 [9.9; 11.6] 443 (82.6)	0.83 [0.72; 0.95]; 0.007
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration[c])					
Fatigue	489	1.45 [1.41; 1.64] 364 (74.4)	496	1.48 [1.41; 2.10] 371 (74.8)	1.02 [0.88; 1.18]; 0.810
Nausea and vomiting	489	2.60 [2.10; 3.22] 301 (61.6)	496	2.60 [2.14; 3.02] 315 (63.5)	0.95 [0.81; 1.12]; 0.570
Pain	489	4.17 [3.48; 5.42] 285 (58.3)	496	3.81 [2.99; 4.40] 304 (61.3)	0.91 [0.77; 1.07]; 0.241
Dyspnoea	489	4.83 [3.78; 5.65] 264 (54.0)	496	4.40 [3.45; 6.21] 273 (55.0)	0.95 [0.80; 1.12]; 0.534
Insomnia	489	5.29 [3.94; 6.93] 251 (51.3)	496	5.78 [4.63; 8.77] 242 (48.8)	1.08 [0.90; 1.29]; 0.407
Appetite loss	489	3.71 [2.79; 4.44] 286 (58.5)	496	4.40 [3.88; 5.62] 264 (53.2)	1.19 [1.00; 1.40]; 0.047
Constipation	489	3.15 [2.73; 4.17] 273 (55.8)	496	3.06 [2.33; 4.80] 276 (55.6)	1.02 [0.86; 1.20]; 0.846
Diarrhoea	489	10.65 [7.62; 14.78] 195 (39.9)	496	11.93 [8.77; 18.17] 191 (38.5)	1.03 [0.84; 1.26]; 0.804
Symptoms (EORTC QLQ-BIL21 – time to first deterioration[c])					
Pain	482	8.58 [6.47; 10.74] 212 (44.0)	490	9.17 [6.97; 11.93] 212 (43.3)	1.02 [0.84; 1.24]; 0.838
Tiredness	482	1.51 [1.41; 2.07] 350 (72.6)	490	2.10 [1.64; 2.69] 338 (69.0)	1.18 [1.01; 1.37]; 0.033
Jaundice	482	4.17 [3.38; 5.32] 275 (57.1)	490	5.13 [3.65; 6.74] 246 (50.2)	1.22 [1.02; 1.45]; 0.027
Eating	482	3.78 [3.48; 4.93] 282 (58.5)	490	4.37 [3.48; 5.32] 269 (54.9)	1.10 [0.93; 1.30]; 0.288

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabin vs. placebo + cisplatin + gemcitabine (multipage table)

Study Outcome category Outcome	Pembrolizumab + cisplatin + gemcitabine		Placebo + cisplatin + gemcitabine		Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
Treatment side effets	482	1.41 [1.35; 1.68] 342 (71.0)	490	1.84 [1.45; 2.27] 329 (67.1)	1.17 [1.01; 1.37]; 0.039
Drains	482	NA 105 (21.8)	490	NR [24.41; NR] 109 (22.2)	1.00 [0.76; 1.31]; 0.995
Health status (EQ-5D VAS, time to first deterioration[e])	491	6.51 [4.86; 9.43] 231 (47.0)	500	8.31 [6.44; 9.36] 234 (46.8)	1.07 [0.89; 1.29]; 0.453
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[d]					
Global health status	489	3.52 [2.79; 4.40] 297 (60.7)	496	2.99 [2.50; 3.71] 310 (62.5)	0.91 [0.77; 1.06]; 0.227
Physical functioning	489	3.48 [2.83; 3.94] 320 (65.4)	496	2.92 [2.69; 3.48] 325 (65.5)	0.97 [0.83; 1.14]; 0.733
Role functioning	489	2.33 [2.07; 2.79] 328 (67.1)	496	2.20 [1.87; 2.73] 346 (69.8)	0.93 [0.80; 1.08]; 0.361
Emotional functioning	489	5.55 [4.27; 8.12] 245 (50.1)	496	6.47 [5.26; 9.89] 225 (45.4)	1.20 [1.00; 1.44]; 0.052
Cognitive functioning	489	3.25 [2.56; 3.71] 294 (60.1)	496	3.09 [2.76; 3.52] 316 (63.7)	0.93 [0.79; 1.09]; 0.363
Social functioning	489	2.17 [2.07; 2.79] 327 (66.9)	496	2.27 [2.10; 2.79] 328 (66.1)	0.99 [0.85; 1.15]; 0.891
EORTC QLQ-BIL21 – time to first deterioration[c]					
Anxiety[f]	482	5.62 [4.83; 7.59] 253 (52.5)	490	8.12 [5.62; 9.79] 227 (46.3)	1.18 [0.99; 1.42]; 0.069
Weight loss[f]	482	11.24 [7.56; NA] 199 (41.3)	490	10.61 [7.56; 15.70] 205 (41.8)	1.02 [0.84; 1.25]; 0.808

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabin vs. placebo + cisplatin + gemcitabine (multipage table)

Study Outcome category Outcome	Pembrolizumab + cisplatin + gemcitabine		Placebo + cisplatin + gemcitabine		Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]

a. Effect estimates and CI: Cox proportional hazards model with treatment as covariate, stratified by region (Asia or non-Asia), disease status (metastatic or locally advanced) and site of origin (hepatic, extrahepatic and gallbladder). In the strata for locally advanced disease status, the characteristic values for the site of origin "gallbladder" and "extrahepatic" were summarized.
b. Wald test.
c. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
d. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. Deviating from the company's approach, this scale was assigned to the health-related quality of life category, rather than the symptoms category.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at le event; N: number of analysed patients; NC: not calculable; NR: not reached; QLQ-BIL21: Quality of Life Questionnaire-Cholangiocarcinoma and Gallbladder Cancer-Specific Module 21; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

Table 16: Results (side effects) – RCT, direct comparison: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine

Study Outcome category Outcome	Pembrolizumab + cisplatin + gemcitabine		Placebo + cisplatin + gemcitabine		Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
KEYNOTE-966					
Side effects[c]					
AEs (supplementary information)	529	524 (99.1)	534	532 (99.6)	-
SAEs	529	276 (52.2)	534	263 (49.3)	1.06 [0.94; 1.19]; 0.530
Severe AEs[d]	529	451 (85.3)	534	449 (84.1)	1.01 [0.96; 1.07]; 0.683
Discontinuation due to AEs	529	138 (26.1)	534	122 (22.8)	1.14 [0.92; 1.41]; 0.248
Immune-related AEs (supplementary information)	529	117 (22.1)	534	69 (12.9)	-
Immune-related SAEs	529	31 (5.9)	534	18 (3.4)	1.74 [0.98; 3.07]; 0.054
Immune-related severe AEs[d]	529	38 (7.2)	534	21 (3.9)	1.83 [1.09; 3.07]; 0.021
Rash (PT, AE)	529	90 (17.0)	534	49 (9.2)	1.85 [1.34; 2.57]; < 0.001
Cardiac disorders (SOC, AE)	529	19 (3.6)	534	7 (1.3)	2.74 [1.16; 6.46]; 0.017
Fever (PT, SAE)	529	30 (5.7)	534	12 (2.2)	2.52 [1.31; 4.88]; 0.004
Neutrophil count decreased (PT, SAE)	529	11 (2.1)	534	1 (0.2)	11.10 [1.44; 85.70]; 0.004
Liver abscess (PT, severe AE[d])	529	4 (0.8)	534	12 (2.2)	0.34 [0.11; 1.04]; 0.047

a. Institute's calculation.
b. Institute's calculation, unconditional exact test (CSZ method according to [15]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
c. The MedDRA terms (PTs) "neoplasm progression", "malignant neoplasm progression" and "disease progression" were not included in the analysis.
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with at least 1 event; N: number of analysed patients; ND no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

On the basis of the available information, at most an indication, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most hints can be derived for all other outcomes due to the high risk of bias and a limited certainty of results.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. This results in an indication of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

Morbidity

Symptoms

EORTC QLQ-C30

Appetite loss

For the outcome of appetite loss, a statistically significant difference was found to the disadvantage of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. For this outcome of the non-serious/non-severe symptoms category, however, the extent of the effect was no more than marginal (see Section I 5.1). This results in no hint of an added or lesser benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, constipation, and diarrhoea

No statistically significant difference between the treatment groups was shown for any of the outcomes “fatigue”, “nausea and vomiting”, “pain”, “dyspnoea”, “insomnia”, “constipation”, and “diarrhoea”. This results in no hint of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

EORTC QLQ-BIL21

Tiredness, jaundice, treatment side effects

For each of the outcomes of tiredness, jaundice, treatment side effects, a statistically significant difference was found to the disadvantage of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. For these outcomes of the non-serious/non-severe symptoms category, however, the extent of the effect was no more than marginal in each case (see Section I 5.1). This results in no hint of an added or lesser benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine in each case; an added benefit is therefore not proven in each case.

Pain, eating, drains

No statistically significant difference between the treatment groups was shown for any of the outcomes of pain, eating, or drains. This results in no hint of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

Health status

There was no statistically significant difference between treatment groups for the outcome of health status. This results in no hint of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BIL21

No statistically significant difference between treatment groups was found for any of the health-related quality of life outcomes. This results in no hint of an added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuations due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. In each case, this results in no hint of greater or lesser harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; greater or lesser harm is therefore not proven.

immune-related severe AEs

For the outcome of immune-related severe AEs, a statistically significant difference was found to the disadvantage of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. This resulted in a hint of greater harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

immune-related SAEs

No statistically significant difference between the treatment groups was shown for the outcome "immune-related SAEs". This results in no hint of greater or lesser harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; greater or lesser harm is therefore not proven.

Specific AEs

Rash (AEs), cardiac disorders (SAEs), fever (SAEs), neutrophil count decreased (SAEs)

For each of the outcomes of rash (AEs), cardiac disorders (SAEs), fever (SAEs), and neutrophil count decreased (SAEs) a statistically significant difference was found to the disadvantage of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. In each case, this resulted in a hint of greater harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

Liver abscess (severe AEs)

For the outcome of liver abscess (severe AEs), a statistically significant difference was found in favour of pembrolizumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. This resulted in a hint of lesser harm from pembrolizumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- age (< 65 years, ≥ 65 years)
- sex (female, male)
- disease status (locally advanced, metastatic)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

For the outcomes “immune-related SAEs” and “immune-related severe AEs”, the company did not present subgroup analyses in the dossier.

Applying the methods described above, there were no effect modifications for the characteristics of age, sex and disease status.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for symptom outcomes

The dossier does not provide any information as to whether the symptoms outcomes (EORTC QLQ-C30 and EORTC QLQ-BIL21) below were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms (EORTC QLQ-C30)

Appetite loss

For the outcome of appetite loss, insufficient severity data are available which would allow classifying them as serious/severe. The outcome was therefore assigned to the outcome category "non-serious/non-severe symptoms/late complications".

Symptoms (EORTC QLQ-BIL21)

Tiredness, jaundice, treatment side effects

For the outcomes of tiredness, jaundice, treatment side effects, the available severity data are insufficient for a classification as serious/severe. The outcomes were therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 17: Extent of added benefit at outcome level: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Observation period **Outcome category** **Outcome**	**Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	Median: 12.7 vs. 10.9 months HR: 0.83 [0.72; 0.95] p = 0.007 Probability: "indication"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ Added benefit; extent: "minor"
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	Median: 1.45 vs. 1.48 months HR: 1.02 [0.88; 1.18] p = 0.810	Lesser/added benefit not proven
Nausea and vomiting	Median: 2.60 vs. 2.60 months HR: 0.95 [0.81; 1.12] p = 0.570	Lesser/added benefit not proven
Pain	Median: 4.17 vs. 3.81 months HR: 0.91 [0.77; 1.07] p = 0.241	Lesser/added benefit not proven
Dyspnoea	Median: 4.83 vs. 4.40 months HR: 0.95 [0.80; 1.12] p = 0.534	Lesser/added benefit not proven
Insomnia	Median: 5.29 vs. 5.78 months HR: 1.08 [0.90; 1.29] p = 0.407	Lesser/added benefit not proven
Appetite loss	Median: 3.71 vs. 4.40 months HR: 1.19 [1.00; 1.40] HR: 0.84 [0.71; 1.00][c,d] p = 0.047	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
Constipation	Median: 3.15 vs. 3.06 months HR: 1.02 [0.86; 1.20] p = 0.846	Lesser/added benefit not proven
Diarrhoea	Median: 10.65 vs. 11.93 months HR: 1.03 [0.84; 1.26] p = 0.804	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Observation period **Outcome category** **Outcome**	**Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Symptoms (EORTC QLQ-BIL21 – time to first deterioration)		
Pain	Median: 8.58 vs. 9.17 months HR: 1.02 [0.84; 1.24] p = 0.838	Lesser/added benefit not proven
Tiredness	Median: 1.51 vs. 2.10 months HR: 1.18 [1.01; 1.37] HR: 0.85 [0.73; 0.99][c] p = 0.033	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
Jaundice	Median: 4.17 vs. 5.13 months HR: 1.22 [1.02; 1.45] HR: 0.82 [0.69; 0.98][c] p = 0.027	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
Eating	Median: 3.78 vs. 4.37 months HR: 1.10 [0.93; 1.30] p = 0.288	Lesser/added benefit not proven
Treatment side effects	Median: 1.41 vs. 1.84 months HR: 1.17 [1.01; 1.37] HR: 0.85 [0.73; 0.99][c] p = 0.039	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
Drains	Median: NR vs. NR HR: 1.00 [0.76; 1.31] p = 0.995	Lesser/added benefit not proven
Health status (EQ-5D VAS, time to first deterioration)	Median: 6.51 vs. 8.31 months HR: 1.07 [0.89; 1.29] p = 0.453	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration		
Global health status	Median: 3.52 vs. 2.99 months HR: 0.91 [0.77; 1.06] p = 0.227	Lesser/added benefit not proven
Physical functioning	Median: 3.48 vs. 2.92 months HR: 0.97 [0.83; 1.14] p = 0.733	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Observation period **Outcome category** **Outcome**	**Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Role functioning	Median: 2.33 vs. 2.20 months HR: 0.93 [0.80; 1.08] p = 0.361	Lesser/added benefit not proven
Emotional functioning	Median: 5.55 vs. 6.47 months HR: 1.20 [1.00; 1.44] p = 0.052	Lesser/added benefit not proven
Cognitive functioning	Median: 3.25 vs. 3.09 months HR: 0.93 [0.79; 1.09] p = 0.363	Lesser/added benefit not proven
Social functioning	Median: 2.17 vs. 2.27 months HR: 0.99 [0.85; 1.15] p = 0.891	Lesser/added benefit not proven
EORTC QLQ-BIL21 – time to first deterioration		
Anxiety	Median: 5.62 vs. 8.12 months HR: 1.18 [0.99; 1.42] p = 0.069	Lesser/added benefit not proven
Weight loss	Median: 11.24 vs. 10.61 months HR: 1.02 [0.84; 1.25] p = 0.808	Lesser/added benefit not proven
Side effects		
SAEs	52.2% vs. 49.3% RR: 1.06 [0.94; 1.19] p = 0.530	Greater/lesser harm not proven
Severe AEs	85.3% vs. 84.1% RR: 1.01 [0.96; 1.07] p = 0.683	Greater/lesser harm not proven
Discontinuation due to AEs	26.1% vs. 22.8% RR: 1.14 [0.92; 1.41] p = 0.248	Greater/lesser harm not proven
immune-related SAEs	5.9% vs. 3.4% RR: 1.74 [0.98; 3.07] p = 0.054	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Observation period **Outcome category** **Outcome**	**Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
immune-related severe AEs	7.2% vs. 3.9% RR: 1.83 [1.09; 3.07] RR: 0.55 [0.33; 0.92][c] p = 0.021 Probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: “minor”
Rash (AEs)	17.0% vs. 9.2% RR: 1.85 [1.34; 2.57] RR: 0.54 [0.39; 0.75][c] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: “considerable”
Cardiac disorders (SAEs)	3.6% vs. 1.3% RR: 2.74 [1.16; 6.46] RR: 0.36 [0.15; 0.86][c] p = 0.017 Probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: “considerable”
Fever (SAEs)	5.7% vs. 2.2% RR: 2.52 [1.31; 4.88] RR: 0.40 [0.20; 0.76][c] p = 0.004 Probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: “considerable”
Neutrophil count decreased (SAEs)	2.1% vs. 0.2% RR: 11.10 [1.44; 85.70] RR: 0.09 [0.01; 0.69][c] p = 0.004 Probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5 % Greater harm, extent: “considerable”
Liver abscess (severe AEs)	0.8% vs. 2.2% RR: 0.34 [0.11; 1.04] p = 0.047 Probability: “hint”	Outcome category: serious/severe side effects Lesser harm[f]; extent: minor[g]

Table 17: Extent of added benefit at outcome level: pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine (multipage table)

Observation period **Outcome category** **Outcome**	**Pembrolizumab + cisplatin + gemcitabine vs. placebo + cisplatin + gemcitabine** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. d. Due to the significant p-value in the Wald test, the unrounded CI_u is < 1.00. e. The extent of the effect in this non-serious/non-severe outcome is no more than marginal. f. The result of the statistical test is decisive for the derivation of added benefit. g. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event		

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of pembrolizumab + cisplatin + gemcitabine vs. cisplatin + gemcitabine

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality • Overall survival: indication of an added benefit – - extent: "minor"	-
Outcomes with shortened observation period	
Serious/severe side effects • Liver abscess (severe AEs): hint of lesser harm – extent: "minor"	Serious/severe side effects • Immune-related severe AEs: hint of greater harm – extent "minor" • Cardiac disorders (SAEs): hint of greater harm – extent "considerable" • Fever (SAE): hint of greater harm – extent "considerable" • Neutrophil count decreased (SAE): hint of greater harm – extent: "considerable"
-	Non-serious/non-severe side effects • Rash (AE): hint of greater harm – extent: "considerable"
AE: adverse event; SAE: serious adverse event	

In summary, both favourable and unfavourable effects of pembrolizumab + cisplatin + gemcitabine were found in comparison with cisplatin + gemcitabine. Only for overall survival are the observed effects based on the entire observation period. For morbidity, health-related quality of life and side effects, in contrast, they are based exclusively on the shortened period (up to 30 or 90 days after the last dose of study medication).

For the favourable effects, there was an indication of minor added benefit for the outcome of overall survival. Furthermore, a hint of lesser harm of minor extent was found for the outcome of liver abscess (severe AEs). On the side of unfavourable effects, there is a hint of lesser harm for immune-related severe AEs and for the specific AEs of cardiac disorders (SAE), fever (SAE), neutrophil count decreased (SAE) and rash (AE) each a hint of considerable harm Overall, the unfavourable effects do not call into question the added benefit in the outcome of overall survival.

In summary, there is an indication of a minor added benefit from pembrolizumab + cisplatin + gemcitabine compared with the ACT cisplatin + gemcitabine for adults with locally advanced unresectable or metastatic biliary tract carcinoma in first-line treatment.

Table 19 summarizes the result of the assessment of added benefit of pembrolizumab + cisplatin + gemcitabine in comparison with the ACT.

Table 19: Pembrolizumab + cisplatin + gemcitabine – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults[b, c]	Cisplatin + gemcitabine (see Appendix VI to Section K of the Pharmaceutical Directive)[d, e]	Indication of minor added benefit

a. Presented is the ACT specified by the G-BA.
b. Only patients with an ECOG PS of 0 or 1 were included in the KEYNOTE-966 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.
c. Based on the therapy carried out in the intervention arm, it is assumed that, in terms of any comorbidities and their general condition, patients are eligible for intensive combination chemotherapy.
d. Necessary measures to eliminate stenoses (especially drainage of the bile ducts) in the study arms remain unaffected.
e. Radiotherapy is not part of the ACT; this does not affect its use as an individualized treatment option.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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