Durvalumab
(biliary tract cancer)

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

EXTRACT

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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.

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
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 Gallbladder Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PGIS	Patient Global Impression of Severity
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query

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 durvalumab. 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 30 March 2023.

Research question

The aim of this report is to assess the added benefit of durvalumab in combination with cisplatin and gemcitabine (hereinafter referred to as durvalumab + cisplatin + gemcitabine) compared with cisplatin in combination with gemcitabine as the appropriate comparator therapy (ACT) in first-line therapy of patients with unresectable or metastatic biliary carcinoma.

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 durvalumab + cisplatin + gemcitabine

Therapeutic indication	**ACT**[a]
First-line treatment of adults with unresectable or metastatic biliary tract cancer in combination with gemcitabine and cisplatin[b]	Cisplatin in combination with gemcitabine, see Section K of the Pharmaceutical Directive, Annex VI.
a. Presented is the ACT specified by the G-BA. b. In light of the therapy carried out in the intervention arm, patients are presumably eligible for intensive combination chemotherapy with regard to their general condition and potential comorbidities. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company named cisplatin in combination with gemcitabine as the ACT, thus following the research question specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of any added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The TOPAZ-1 study was used for the benefit assessment of durvalumab + cisplatin + gemcitabine. It is a double-blind RCT comparing durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine in the first-line treatment of adults with unresectable or metastatic biliary carcinoma. The study enrolled patients who had not previously received

systemic therapy for this stage of the disease. Patients with previous curative chemotherapy or radiotherapy were eligible for inclusion in case of disease recurrence if the therapy had been completed at least 6 months prior to randomization. Patients with brain metastases were excluded from the study. Patients had to be in general health rated as 0 or 1 on the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and exhibit normal bone marrow and organ function. Due to these criteria, the TOPAZ-1 study offers no data on patients with brain metastases or with ECOG-PS > 1.

The TOPAZ-1 study enrolled a total of 180 patients in 2 cohorts (see below for a detailed description) and randomized them to the treatment arms in a 1:1 ratio. A total of 405 patients were randomly assigned to the intervention arm and 405 patients to the comparator arm. Allocation was stratified according to disease status (initially inoperable or recurrent) and primary tumour location (intrahepatic, extrahepatic, bile duct carcinoma, or gallbladder carcinoma).

Patients in both arms received cisplatin + gemcitabine chemotherapy on Days 1 and 8 of 3-week cycles for a total of 8 cycles or a maximum of 24 weeks. Day 1 of each cycle involved the additional administration of durvalumab in the intervention arm and placebo in the control arm. After the end of chemotherapy, durvalumab or placebo was administered as monotherapy in a 4-week cycle, each on Day 1.

The primary outcome of the TOPAZ-1 study was overall survival. Patient-relevant secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Cohorts of the TOPAZ-1 study

For the benefit assessment, the company presented a pooled analysis based on individual patient data from 2 cohorts, the global cohort and the China extension cohort. According to the company, the expansion cohort was recruited separately for the purpose of obtaining a marketing authorization for durvalumab in China. As per study protocol, the China extension cohort was recruited after completion of the recruitment phase for the global cohort. Almost identical study protocols and statistical analysis plans (SAP) were used for patients in the China extension cohort and the global cohort.

The global cohort included 685 patients, 341 in the intervention arm and 344 in the comparator arm. In the China extension cohort, 125 patients were randomly assigned to the treatment arms, 64 to the intervention arm and 61 to the comparator arm.

The company's dossier presents neither the study report for the China extension cohort nor separate data for the 2 cohorts in Module 4. The company likewise provides no information as to why no study report is yet available for the Chinese cohort (14 October 2022 data cutoff).

Data cutoffs and available analyses

The data cutoffs for the 2 cohorts of the TOPAZ-1 study were planned and carried out separately. The data cutoffs available for the respective cohorts or data cutoffs included in the pooled analyses are presented below.

Data cutoffs available for the global cohort in the dossier:

- 11 August 2021 data cutoff: predefined interim analysis of overall survival planned to be implemented after about 397 events. Since, at that point, there was already a statistically significant result for the outcome of overall survival in favour of durvalumab, this data cutoff simultaneously represents the final analysis.
- 25 February 2022 data cutoff: analysis of the extended follow-up of overall survival and side effects at the time of the originally planned final analysis.

A final analysis of overall survival was planned to be conducted for the global cohort after around 496 events. However, since the interim analysis of 11 August 2021 already showed a statistically significant result in favour of durvalumab, this analysis represents the final analysis of the study as per study protocol. After this data cutoff, a protocol amendment was enacted to introduce an extended follow-up of overall survival and side effects. The 25 February 2022 data cutoff was implemented around the time when the originally scheduled final analysis should have taken place. De facto, the timing (necessary number of events) for this data cutoff had therefore already been determined before the start of the study.

Available data cutoffs for the China expansion cohort:

- 14 October 2022 data cutoff: predefined data cutoff to evaluate overall survival at the same proportion of events where a statistically significant difference was found in the global cohort.

The pooled analyses of the 2 cohorts presented in Module 4 are based on the following data cutoffs for the various outcomes:

- Outcomes in the category of overall survival and side effects:
  - global cohort: 25 February 2022 data cutoff
  - China expansion cohort: 14 October 2022 data cutoff
- Outcomes of the categories of morbidity and health-related quality of life:
  - global cohort: 11 August 2021 data cutoff
  - China expansion cohort: 14 October 2022 data cutoff

The pooled analyses of the 2 cohorts presented by the company were used for the benefit assessment.

Risk of bias

The risk of bias across outcomes is rated as low for the TOPAZ-1 study.

The risk of bias at the outcome level for the outcomes of symptoms (symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30], European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cholangiocarcinoma and Gallbladder Cancer [EORTC QLQ-BIL21], and Patient Global Impression of Severity [PGIS]), health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]), and health-related quality of life (functional scales of the EORTC QLQ-C30 and EORTC QLQ-BIL21) is rated as high due to incomplete observations for potentially informative reasons. For the patients included in the analysis, the return rates of the respective questionnaires decreased markedly over time in both treatment arms.

The risk of bias for the outcomes of the side effects category was rated as high. For the mentioned outcomes in the side effects category, observations are incomplete because the follow-up observation was not complete. The reasons for discontinuation are potentially informative, and some of them differ between study arms.

The certainty of results for the outcome of discontinuation due to adverse events (AEs) is limited despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs which would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Results

Mortality

Overall survival

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

Morbidity

Symptoms (EORTC QLQ-C30)

No statistically significant difference between treatment groups was found for any of the EORTC QLQ-C30 symptom scales. This results in no hint of an added benefit of durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-BIL21)

Difficulties with drainage

For the outcome of difficulties with drainage, there was a statistically significant difference between treatment groups to the disadvantage of durvalumab + cisplatin + gemcitabine. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms / late complications was no more than marginal. This results in no hint of an added or lesser benefit of durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; an added benefit is therefore not proven.

Pain, fatigue, jaundice, difficulty eating, and side effects of treatment

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

Symptoms (PGIS)

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

Health status (EQ-5D VAS)

There was no statistically significant difference between treatment groups for the outcome of EQ-5D VAS. This results in no hint of an added benefit of durvalumab + 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 durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation 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 durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; greater or lesser harm is therefore not proven.

Immune-related SAEs and immune-related severe AEs (CTCAE grade 3-4)

No statistically significant difference between the treatment groups was shown for either of the outcomes of immune-related SAEs or immune-related severe AEs (CTCAE grade 3 to 4). In each case, this results in no hint of greater or lesser harm from durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; greater or lesser harm is therefore not proven.

Specific AEs

Diseases of the skin and subcutaneous tissue (AEs), fever (AEs), anaemia (AEs), and cholangitis (severe AEs)

For each of the outcomes of skin and subcutaneous tissue disorders (AEs), fever (SAEs), anaemia (SAEs), and cholangitis (severe AEs), a statistically significant difference was found to the disadvantage of durvalumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. In each case, this results in a hint of greater harm from durvalumab + 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 probability and extent of added benefit of the drug durvalumab in comparison with the ACT is assessed as follows:

Overall, both favourable and unfavourable effects of durvalumab + cisplatin + gemcitabine were found in comparison with the ACT.

[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].

For the favourable effects, there was an indication of major added benefit for the outcome of overall survival. For the unfavourable effects, the specific AEs of fever (AE), anaemia (AE), cholangitis (severe AE), and skin and subcutaneous tissue disorders (AEs) each show a hint of minor or considerable harm.

In summary, there is an indication of considerable added benefit for adult patients with unresectable or metastatic biliary carcinoma in first-line therapy compared with the ACT of cisplatin in combination with gemcitabine.

Table 3 shows a summary of the probability and extent of added benefit of durvalumab.

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

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of adults with unresectable or metastatic biliary tract cancer in combination with gemcitabine and cisplatin	Cisplatin in combination with gemcitabine[b] see Appendix VI to Section K of the Pharmaceutical Directive.	Indication of considerable added benefit
a. Presented is the respective ACT specified by the G-BA. b. In light of the therapy carried out in the intervention arm, patients are presumably eligible for intensive combination chemotherapy with regard to their general condition and potential comorbidities. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for deriving 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 durvalumab in combination with cisplatin and gemcitabine (hereinafter referred to as durvalumab + cisplatin + gemcitabine) compared with cisplatin in combination with gemcitabine as an ACT in patients with unresectable or metastatic biliary carcinoma in first-line therapy.

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 durvalumab + cisplatin + gemcitabine

Therapeutic indication	**ACT**[a]
First-line treatment of adults with unresectable or metastatic biliary tract cancer in combination with gemcitabine and cisplatin[b]	Cisplatin in combination with gemcitabine, see Section K of the Pharmaceutical Directive, Annex VI.
a. Presented is the ACT specified by the G-BA. b. In light of the therapy carried out in the intervention arm, patients are presumably eligible for intensive combination chemotherapy with regard to their general condition and potential comorbidities. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company named cisplatin in combination with gemcitabine as the ACT and thus followed the G-BA's specification.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs were used for the derivation of 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 durvalumab (status: 4 January 2023)
- bibliographical literature search on durvalumab (last search on 3 January 2023)
- search in trial registries / trial results databases for studies on durvalumab (last search on 2 January 2023)
- search on the G-BA website for durvalumab (last search on 5 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on durvalumab (last search on 12 April 2023); for search strategies, see Appendix I A of the full dossier assessment

No additional relevant study was identified from the check of the completeness of the study pool.

I 3.1 Study included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + 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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
D933AC00001 (TOPAZ-1[d])	Yes	Yes	No	Yes[e] [3]	Yes [4-7]	Yes [8]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. No study report is available for the China expansion cohort.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The TOPAZ-1 study was used for the benefit assessment. The study pool concurs with that of 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: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TOPAZ-1	RCT, double-blind, parallel	▪ Adult patients (≥ 18 years of age) with advanced, unresectable, or metastasized biliary carcinoma in first-line treatment or in whom a recurrence has occurred after adjuvant chemotherapy (> 6 months since completion) ▪ ECOG-PS ≤ 1	Durvalumab + cisplatin + gemcitabine (N = 405)[b] Placebo + cisplatin + gemcitabine (N = 405)[b]	Screening: 28 days prior to the start of treatment Treatment: ▪ Durvalumab: until confirmed disease progression (RECIST version 1.1), clinical progression, unacceptable toxicity, or another discontinuation criterion ▪ Gemcitabine / cisplatin: maximum of 8 cycles Observation[c]: outcome-specific, at most until death or end of study	121 centres in Argentina, Bulgaria, Chile, China, France, Great Britain, Hong Kong, India, Italy, Japan, Poland, Russia, South Korea, Taiwan, Thailand, Turkey, United States, 4/2019 – ongoing Data cutoffs for global cohort: ▪ 11/08/2021[d] ▪ 25/02/2022[e] Data cutoffs for extension cohort: ▪ 14/10/2022[f]	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

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. The number of randomized patients is based on 2 pooled cohorts. The global cohort with 685 patients, 341 in the intervention arm and 344 in the control arm, and the China extension cohort with a total of 125 patients, 64 in the intervention arm and 61 in the control arm.
c. Outcome-specific information is provided in Table 8.
d. Data cutoff planned a priori for outcomes from the categories of overall survival, morbidity, health-related quality of life, and side effects of the global cohort.
e. Data cutoff of the extended follow-up for outcomes of the categories of overall survival and side effects from the global cohort.
f. Planned final data cutoff of the China extension cohort for the outcomes from the categories of overall survival, morbidity, health-related quality of life, and side effects.

AE: adverse event; ECOG-PS: Eastern Cooperative of Oncology Group Performance Status; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine

Study	Intervention	Comparison
TOPAZ-1	8 cycles Durvalumab 1500 mg[a] i.v. every 21 days + on Days 1 and 8 every 21 days: ▪ gemcitabine 1000 mg/m^2 BSA, i.v. ▪ cisplatin 25 mg/m^2 BSA, i.v. Maintenance therapy From Cycle 8 after treatment start durvalumab monotherapy 1500 mg[b] i.v. on Day 1 of a 4-week cycle	8 cycles Placebo i.v., every 21 days + on Days 1 and 8 every 21 days: ▪ gemcitabine 1000 mg/m^2, i.v. BSA ▪ cisplatin 25 mg/m^2, i.v. BSA Maintenance therapy From Cycle 8 after treatment start placebo monotherapy i.v. on Day 1 of a 4-week cycle
	▪ Treatment was to be administered until demonstration of disease progression as per RECIST version 1.1, but it could be continued at the investigator's discretion if patients derived clinical benefit from the treatment. ▪ If chemotherapy was discontinued due to toxicity, continuation of durvalumab treatment or placebo was allowed as soon as toxicity decreased to CTCAE ≤ grade 2. ▪ Treatment interruptions due to toxicity were possible. Dose adjustments: Dose reduction was allowed only for cisplatin and gemcitabine.	
	Allowed prior treatment ▪ Systemic adjuvant chemotherapy and/or radiotherapy with curative intent > 6 months before randomization **Disallowed prior treatment** ▪ Other monoclonal antibodies such as PD-1, PD-L1, or CTLA-4 inhibitors ▪ Systemic immunosuppressive therapies 14 days before the 1st study medication (except systemic glucocorticoids < 10 mg/day prednisone equivalent) ▪ Surgical interventions at the investigator's discretion < 28 days before the first study medication ▪ Live vaccines within 30 days prior to the first dose of study medication **Allowed concomitant treatment** ▪ Antibiotics, nutritional support, correction of metabolic disorders, optimized symptom control, and pain therapy (including radiotherapy of non-target lesions) **Disallowed concomitant treatment** ▪ Any other concurrently administered chemotherapy, radiotherapy, immunotherapy, or biological or hormonal therapy for oncological treatment other than the investigational therapy ▪ Systemic immunosuppressive therapy (except systemic glucocorticoids < 10 mg/day prednisone equivalent) ▪ EGFR tyrosine kinase inhibitors until 90 days after the last dose of study medication ▪ Live vaccines until 30 days after the last dose of study medication ▪ Herbs and natural remedies with possible immunomodulatory effects in the intervention arm only after approval by the sponsor	

a. Patients with a body weight ≤ 30 kg received durvalumab at a weight-dependent dose of 20 mg/kg body weight.

BSA: body surface area; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; EGFR: epidermal growth factor receptor; i.v. intravenous; PD-L1/2: programmed cell death ligand 1/2; RCT: randomized controlled trial, RECIST: Response Evaluation Criteria in Solid Tumours

The TOPAZ-1 study is a double-blind RCT comparing durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine in the first-line treatment of adults with unresectable or metastatic biliary carcinoma. The study enrolled patients who had not previously received systemic therapy for this stage of the disease. Patients with previous curative chemotherapy or radiotherapy were eligible for inclusion in case of disease recurrence if the therapy had been completed at least 6 months prior to randomization. Patients with brain metastases were excluded from the study. Patients had to be in general health rated as 0 or 1 on the ECOG-PS and exhibit normal bone marrow and organ function. Due to these criteria, the TOPAZ-1 study offers no data on patients with brain metastases or with ECOG-PS > 1.

The TOPAZ-1 study enrolled a total of 180 patients in 2 cohorts (see below for a detailed description) and randomized them to the treatment arms in a 1:1 ratio. A total of 405 patients were randomly assigned to the intervention arm and 405 patients to the comparator arm. Allocation was stratified according to disease status (initially inoperable or recurrent) and primary tumour location (intrahepatic, extrahepatic, bile duct carcinoma, or gallbladder carcinoma).

Patients in both arms received cisplatin + gemcitabine chemotherapy on Days 1 and 8 of 3-week cycles for a total of 8 cycles or a maximum of 24 weeks. Day 1 of each cycle involved the additional administration of durvalumab in the intervention arm and placebo in the control arm. After the end of chemotherapy, durvalumab or placebo was administered as monotherapy in a 4-week cycle, each on Day 1. In both treatment arms, the drugs were administered in line with the SPC [9-11].

Treatment was administered until disease progression (clinical or as determined by RECIST version 1.1), unacceptable toxicity, initiation of other tumour therapy, withdrawal of consent, or death. In deviation from the approval of durvalumab, continuing treatment with durvalumab or placebo was allowed at the investigator's discretion beyond progression as per RECIST criteria, provided that patients still clinically benefited in the investigator's opinion. Patients in the comparator arm were not allowed to switch to the intervention arm treatment.

The primary outcome of the TOPAZ-1 study was overall survival. Patient-relevant secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Cohorts of the TOPAZ-1 study

For the benefit assessment, the company presented a pooled analysis based on individual patient data from 2 cohorts, the global cohort and the China extension cohort. According to the company, the expansion cohort was recruited separately for the purpose of obtaining a marketing authorization for durvalumab in China. As per study protocol, the China extension cohort was recruited after completion of the recruitment phase for the global cohort. Almost

identical study protocols and SAPs were used for patients in the China extension cohort and the global cohort.

The global cohort included 685 patients, 341 in the intervention arm and 344 in the comparator arm. In the China extension cohort, 125 patients were randomly assigned to the treatment arms, 64 to the intervention arm and 61 to the comparator arm.

The company's dossier presents neither the study report for the China extension cohort nor separate data for the 2 cohorts in Module 4. The company likewise provides no information as to why no study report is yet available for the Chinese cohort (14 October 2022 data cutoff).

Data cutoffs and available analyses

The data cutoffs for the 2 cohorts of the TOPAZ-1 study were planned and carried out separately. The data cutoffs available for the respective cohorts or data cutoffs included in the pooled analyses are presented below.

Data cutoffs available for the global cohort in the dossier:

- 11 August 2021 data cutoff: predefined interim analysis of overall survival planned to be implemented after about 397 events Because at that point, there was already a statistically significant result for the outcome of overall survival in favour of durvalumab, this data cutoff simultaneously represents the final analysis.
- 25 February 2022 data cutoff: analysis of the extended follow-up of overall survival and side effects at the time of the originally planned final analysis.

A final analysis of overall survival was planned to be conducted for the global cohort after around 496 events. However, since the interim analysis of 11 August 2021 already showed a statistically significant result in favour of durvalumab, this analysis represents the final analysis of the study as per study protocol. After this data cutoff, a protocol amendment introduced an extended follow-up of overall survival and side effects. The 25 February 2022 data cutoff based on the above was implemented around the time when the originally planned final analysis should have taken place. De facto, the timing (necessary number of events) for this data cutoff was therefore already determined before the start of the study. Hence, this data cutoff is presumably not subject to a significantly higher risk of bias than the 11 August 2021 data cutoff.

Available data cutoffs for the China expansion cohort:

- 14 October 2022 data cutoff: predefined data cutoff to evaluate overall survival at the same proportion of events where a statistically significant difference was found in the global cohort.

The pooled analyses of the 2 cohorts presented in Module 4 are based on the following data cutoffs for the various outcomes:

- Outcomes in the category of overall survival and side effects:
  - global cohort: 25 February 2022 data cutoff
  - China expansion cohort: 14 October 2022 data cutoff
- Outcomes of the categories of morbidity and health-related quality of life:
  - global cohort: 11 August 2021 data cutoff
  - China expansion cohort: 14 October 2022 data cutoff

The pooled analyses of the 2 cohorts presented by the company were used for the benefit assessment.

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: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine

Study **Outcome category** **Outcome**	**Planned follow-up observation**
TOPAZ-1	
Mortality	
Overall survival	Until death or termination of study by the sponsor
Morbidity	
Symptoms (EORTC QLQ-C30; EORTC QLQ-BIL21, PGIS) Health status (EQ-5D VAS) Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BIL21)	Up to 90 days after the last dose of study medication in case of treatment discontinuation due to progression; in the event of discontinuation for other reasons, until progression, death, start of subsequent therapy, or study discontinuation[a]
Side effects	
All outcomes in the side effects category	Until 90 days after the last dose of study drug or start of a subsequent therapy

a. If therapy was discontinued or completed without disease progression as per RECIST version 1.1, follow-up was conducted every 6 weeks for the first 24 weeks and then every 8 weeks until progression, start of subsequent therapy, or death.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-BIL21: Quality of life Questionnaire – Cholangiocarcinoma and Gallbladder Cancer 21; QLQ-C30: Quality of life Questionnaire – Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes of morbidity, health-related quality of life, and side effects were systematically shortened because they were recorded only for the period of treatment with the study medication (plus 90 days). Only patients who showed no disease progression at any point of the study or who received no follow-up therapy were followed up until death. This applies to only a very small proportion of patients. However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record all outcomes for the total period, as was done for survival.

Characteristics of the patient population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the pooled cohorts as well as study/treatment discontinuation – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (multipage table)

Study **Characteristic** **Category**	**Durvalumab + cisplatin + gemcitabine** **N = 405**	**Placebo + cisplatin + gemcitabine** **N = 405**
TOPAZ-1		
Age [years], mean (SD)	62 (10.5)	62 (10.9)
Sex [f/m], %	50.9/49.1	48.6/51.4
Family origin, n (%)		
Asian	249 (61.5)	262 (64.7)
White	131 (32.3)	124 (30.6)
African-American or Black	8 (2.0)	6 (1.5)
Native American or Alaska Native	0	1 (0.2)
Other	17 (4.2)	12 (3.0)
Region[a]		
Asia	242 (59.8)	257 (63.5)
Rest of the world	163 (40.2)	148 (36.5)
ECOG-PS, n (%)		
0	189 (46.7)	185 (45.7)
1	216 (53.3)	220 (54.3)
Initially not resectable, n (%)	329 (81.2)	334 (82.5)
Recurrence, n (%)	76 (18.8)	70 (17.3)
Primary tumour location		
iCCA	236 (58.3)	235 (58.0)
eCCA	73 (18.0)	72 (17.8)
GBC	96 (23.7)	98 (24.2)

Table 9: Characteristics of the pooled cohorts as well as study/treatment discontinuation – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (multipage table)

Study Characteristic Category	**Durvalumab + cisplatin + gemcitabine N = 405**	**Placebo + cisplatin + gemcitabine N = 405**
Stage of disease, n (%)		
Locally advanced	55 (13.6)	73 (18.0)
Metastatic	350 (86.4)	331 (81.7)
Missing	0	1 (0.2)
PD-L1 expression, n (%)		
High (TAP ≥ 1%)	239 (59.0)	251 (62.0)
Low/Negative (TAP < 1%)	119 (29.4)	117 (28.9)
Missing	47 (11.6)	37 (9.1)
Number of prior chemotherapies, n (%)		
0	381 (94.1)	372 (91.9)
1	23 (5.7)	31 (7.7)
2	1 (0.2)	2 (0.5)
Previous surgical/interventional procedures related to the investigated disease (except stenting and drainage of the biliary tract)[a], n (%)		
Curative surgery	75 (18.5)	70 (17.3)
Noncurative surgery	25 (6.2)	35 (8.6)
Treatment discontinuation, n (%)[b]	336 (83.0)[d]	380 (93.8)[d]
Study discontinuation, n (%)[c]	245 (60.5)[d]	282 (69.6)[d]

a. Patients with several interventions in 1 category are counted once. Patients with several interventions in different categories are counted once per category.
b. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression as per RECIST 1.1 (64% vs. 71%) and AEs (8.3% vs. 5.7%).
c. Common reasons for study discontinuation in the intervention arm versus control arm were patient death (98% versus 96%) and treatment discontinuation as per patient decision (1% versus 4%).
d. Institute's calculation.

eCCA: extrahepatic cholangiocarcinoma; f: female; GBC: gallbladder cancer; iCCA: intrahepatic cholangiocarcinoma; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SD: standard deviation; TAP: tumour cell positivity

The patient characteristics of the pooled cohorts are largely comparable between the 2 treatment arms. The mean age of the patients was 62 years. About 60% of the patients came from Asia. The majority of patients had intrahepatic carcinoma (58%), around 24% had extrahepatic bile duct carcinoma, and 18% had gallbladder carcinoma. The majority of patients in both arms were diagnosed with an initially unresectable tumour (82%). Before

study start, curative chemotherapy was received by 5.7% of patients in the intervention arm and 7.7% in the control arm, compared to around 18% in both arms receiving curative surgery.

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine

Study **Duration of the study phase** **Outcome category**	**Durvalumab + cisplatin + gemcitabine** **N = 405**	**Placebo + cisplatin + gemcitabine** **N = 405**
TOPAZ-1		
Treatment duration[a] [months]		
Durvalumab/Placebo + cisplatin + gemcitabine		
Median [min; max]	5.52 [0.1; 9.0]	5.49 [0.2; 8.1]
Mean (SD)	4.44 (1.84)	4.25 (1.78)
Durvalumab/Placebo + cisplatin + gemcitabine and subsequent durvalumab/placebo monotherapy		
Median [min; max]	6.67 [0.1; 24.5]	5.59 [0.2; 21.5]
Mean (SD)	6.87 (4.69)	5.76 (3.61)
Observation period [months]		
Overall survival[b]		
Median [min; max]	12.45 [0.1; 33.2]	10.68 [0.2; 32.5]
Mean (SD)	ND	ND
Morbidity[a]		
EORTC QLQ-C30, EQ-5D VAS, PGIS		
Median [min; max]	5.16 [0.0; 23.2]	4.73 [0.0; 21.3]
Mean (SD)	ND	ND
EORTC QLQ-BIL21		
Median [min; max]	4.96 [0.0; 23.2]	4.63 [0.0; 21.3]
Mean (SD)	ND	ND
Health-related quality of life[a]		
EORTC QLQ-C30		
Median [min; max]	5.16 [0.0; 23.2]	4.73 [0.0; 21.3]
Mean (SD)	ND	ND
EORTC QLQ-BIL21		
Median [min; max]	4.96 [0.0; 23.2]	4.63 [0.0; 21.3]
Mean (SD)	ND	ND
Side effects[b]		
Median [min; max]	7.92 [0.1; 31.1]	6.97 [0.2; 26.8]
Mean (SD)	ND	ND

a. Data cutoffs of the pooled cohort: 11/08/2021 (global cohort) and 14/10/2022 (China expansion cohort)
b. Data cutoffs of the pooled cohort: 25/02/2022 (global cohort) and 14/10/2022 (China expansion cohort)

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; ITT: intention to treat; max.: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-BIL2128: Quality of Life Questionnaire-Cholangiocarcinoma and Gallbladder Cancer 21; RCT: randomized controlled trial; SAS: safety analysis set; SD: standard deviation; VAS: visual analogue scale

The median treatment duration for the pooled cohort was similar in both treatment arms, being about 1 month longer in the intervention arm than in the comparator arm (6.67 months versus 5.59 months).

In all patients who discontinued the study due to disease progression, outcomes of the morbidity and health-related quality of life categories were planned to be observed for only up to 90 days after the last dose of the study drug. Given the available data, the median observation period is nevertheless comparable for the outcome of overall survival as well as for the outcomes from the categories of morbidity and health-related quality of life.

Information on subsequent therapies

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

Table 11: Information on antineoplastic subsequent therapies – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (TOPAZ-1 study)

Study **Drug class**	**Patients with subsequent therapy n (%)**	
	Durvalumab + cisplatin + gemcitabine **N = 405**	**Placebo + cisplatin + gemcitabine** **N = 405**
TOPAZ-1		
Total[a]	171 (42.2)	192 (47.4)
Cytotoxic chemotherapy	152 (37.5)	165 (40.7)
Taxane chemotherapy	10 (2.5)	17 (4.2)
Targeted therapy	26 (6.4)	31 (7.7)
Immunotherapy	19 (4.7)	26 (6.4)
Antiangiogenic chemotherapy	4 (1.0)	2 (0.5)
Other	23 (5.7)	35 (8.6)

a. It was possible for patients to receive more than 1 therapy.

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

Switching from the comparator to the intervention arm after disease progression was not allowed. Furthermore, subsequent therapy was allowed without restrictions in both study arms. The proportion of patients receiving subsequent therapy was balanced between the treatment arms in both cohorts. Overall, 42.2% of the patients in the intervention arm and 47.4% of the patients in the control arm received subsequent antineoplastic therapy. The most commonly received therapy was cytotoxic chemotherapy (37.5% versus 40.7%). Far fewer patients received targeted (6.4% versus 7.7%), immunological (4.7% versus 6.4%), or anti-

angiogenic (1% versus 0.5%) subsequent therapies. The proportion of therapies used was comparable between the treatment arms.

The company presents the subsequent therapies exclusively according to drug classes. A more detailed assessment, however, would require information on the individual drug used. Overall, the subsequent therapies used in the TOPAZ-1 study are in line with the treatment options presented in the S3 guideline [12]. For patients in good general health, the guideline recommends a treatment regimen with oxaliplatin or irinotecan after failure of first-line therapy. In addition, a molecular tumour board is indicated to determine possible molecular genetic therapeutic approaches.

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: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
TOPAZ-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the TOPAZ-1 study.

Transferability of the study results to the German health care context

The company stated that TOPAZ-1 study was deemed representative for the German health care context with regard to demographic and disease-specific factors. Reportedly, the age distribution and gender ratio support this view. The company argues that the study medication and the subsequent therapies were in line with the recommendations issued in the German S3 guideline on diagnosis and therapy of hepatocellular carcinoma and biliary carcinomas [12] and correspond to the standard of care.

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 surveyed using the EORTC QLQ-C30), the EORTC QLQ-BIL21, and the PGIS
  - health status, surveyed 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 and severe AEs (CTCAE grade 3 to 4)
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-BIL21, and PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BIL21)	SAEs	Heavy AEs[a]	Discontinuation due to AEs[b]	Immune-related SAEs[c]	Immune-related severe AEs[c, d]	Further specific AEs[e]
TOPAZ-1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Discontinuation of 1 or more treatment components.
c. The results from the predefined operationalization of AEs of special interest is used in each case. The results from the global cohort are relevant for the assessment (see Section I 4.1).
d. Immune-mediated severe AEs are operationalized as CTCAE grade 3 to 4.
e. The following events were taken into account (MedDRA coding): skin and subcutaneous tissue disorders (SOC, AEs), anaemia (PT, SAEs), fever (PT, SAEs), cholangitis (PT, severe AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PGIS: Patient Global Impression of Severity; PT: Preferred Term; QLQ-BIL21: Quality of Life Questionnaire – Cholangiocarcinoma and Gallbladder Cancer 21; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Symptoms, health status, and health-related quality of life

Operationalization of the instruments EORTC QLQ-C30, QLQ-BIL21, and EQ-5D VAS

In its dossier, the company presents analyses for the outcomes of morbidity and health-related quality of life regarding the time to first deterioration by 10 points (EORTC QLQ-C30 and QLQ-BIL21) and by 15 points (EQ-5D VAS). However, the study protocol predefined the operationalization of time to confirmed deterioration (on 2 consecutive visits) for these outcomes. A deterioration was to be deemed confirmed even if it occurred during the last available survey. The company does not justify its approach, which deviates from the study protocol. If the observation period is sufficiently long to achieve a confirmed deterioration and if the observation times between the treatment arms are sufficiently similar, the analysis of confirmed deterioration is meaningful in terms of content as well as being usable for the benefit assessment. The same is described by the G-BA in the "Answers to frequently asked questions on the benefit assessment procedure" [13]. In the TOPAZ-1 study, the observation periods between the treatment arms for the outcomes of morbidity and health-related quality of life are sufficiently similar and sufficiently long (see Table 10). The available data do not

show how many patients in the TOPAZ-1 study exhibited a deterioration only at the last survey time. However, the operationalization of first deterioration as presented by the company is generally suitable and was used for the benefit assessment.

Outcome category of the EORTC QLQ-BIL21

In the health-related quality of life 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 side effects of therapy, difficulties with drainage, and worry about weight loss are each 1-item scales. Unlike the company, this assessment assigned the scales of eating, jaundice, tiredness, pain, and difficulties with drainage to the outcome category of symptoms. Like the company, it assigned the scales anxiety and worry about weight loss to the health-related quality of life category.

Symptoms surveyed with the instrument PGIS

The PGIS is a patient-reported 1-item instrument for recording the severity of symptoms or symptom complexes (selectable depending on the underlying disease) on a scale from 0 (no symptoms) to 6 (very severe symptoms). Higher values are associated with more severe patient symptoms. The PGIS represents a patient-relevant outcome.

For the present benefit assessment, the company presents the operationalization of first deterioration to 5 points (severe symptoms) or 6 points (very severe symptoms). This is used for the assessment.

Side effects

Types of analysis

For the outcome category of side effects, the company analysed time to event, presenting the hazard ratio (HR) as the effect measure. It justifies this approach with different observation durations between the treatment arms. However, the observation durations are deemed to be sufficiently similar (see Table 10). In the assessment of side effects, it is primarily relevant in how many patients an event occurred. In addition, when analysing time until occurrence of the event, effects may result solely from an earlier or later occurrence of the event or on the basis of proportions. For this reason, the analyses of relative risk (RR) are used in the present assessment to derive added benefit.

Survey of the progression of the underlying disease in the outcomes of SAEs and discontinuation due to AEs

The TOPAZ-1 study protocol defines that AEs which can be attributed to the progression or symptoms of the underlying disease are not recorded as AEs unless they are a SAEs or a

discontinuation due to AEs. The company did not eliminate these events from the analyses of SAEs or discontinuations due to AEs. However, the available information does not show events which could potentially be attributed to the progression of the underlying disease to have a relevant impact on the interpretability of the analyses.

Note on immune-mediated AEs

Immune-mediated AEs are a relevant aspect of the side effect profile of PD-L1 inhibitors such as durvalumab. However, the company's Module 4 does not present analyses on immune-mediated AEs.

Operationalization

To draw conclusions on immune-mediated AEs, the present benefit assessment uses the AEs of special interest (AESIs) prespecified in the TOPAZ-1 study.

In the TOPAZ-1 study, AESIs served as the baseline set for the identification of immune-mediated AEs. The TOPAZ-1 study protocol describes categories for the recording of AESI. According to the study protocol, these categories are side effects for which (with the exception of infusion-related reactions) an immune-mediated reaction is assumed to be the potential cause:

- diarrhoea/colitis/ gastrointestinal perforation
- pneumonitis
- hepatic events
- endocrinopathies (e.g. hypophysitis, adrenal insufficiency)
- hyperthyroidism and hypothyroidism, thyroiditis
- type 1 diabetes mellitus
- rash/dermatitis
- renal events
- pancreatic events
- myocarditis
- myositis
- rare or less frequent immune-mediated AEs such as immune thrombocytopenia and AEs including neuromuscular toxicity (e.g. Guillain-Barré syndrome, myasthenia gravis)
- infusion-related reaction and hypersensitivity

The dossier's Module 4 presents AESI results for the pooled cohort which show that the company deviates from the AESIs predefined in the study protocol by additionally including in the analysis predefined standardized MedDRA queries (SMQs) (liver diseases, biliary diseases, haematopoietic cytopenias). These SMQs in part reflect symptoms of the underlying disease (liver diseases, biliary diseases) and side effects of chemotherapy (haematopoietic cytopenias) but are not relevant for the assessment of immune-mediated AEs. The analyses submitted by the company in Module 4 are therefore unusable. In the present situation, immune-mediated AEs are assessed using the analyses of the AESIs predefined in the study protocol which occurred in the global cohort by the 25 February 2022 data cutoff. No separate data are available on AESIs in the China expansion cohort.

Notes on the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument

As per study protocol, the TOPAZ-1 study also surveyed side effects using the PRO-CTCAE instrument for descriptive purposes. Overall, the PRO-CTCAE system is a valuable addition to the usual survey and analysis of AEs. The system comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection process is to be planned a priori and carried out transparently. The selection of the individual symptomatic AEs, e.g. the recording of all important potential AEs of the drugs in the intervention and control arms, must be plausible. For a comprehensive description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [14]. As per study protocol, 6 symptomatic AEs from the PRO-CTCAE system were to be surveyed in the TOPAZ-1 study:

- mouth/throat sores
- shortness of breath
- cough
- rash
- hair loss
- numbness and tingling in hands and feet

The company reports that it made its selection by comparing the usual side effects of the 3 drugs investigated in the study. It also excludes the AEs already queried in the EORTC modules. The company does not provide more detailed information on its approach, e.g. on the search or the type of documents reviewed. Based on the information provided by the company, however, it presumably did not implement the approaches described in A20-87 [14] for selecting the items according to Tolstrup [15] or Taarnhøj [16]. All 6 selected symptomatic

AEs represent known side effects of cisplatin or gemcitabine. However, it is not possible to determine whether side effects of durvalumab are adequately depicted.

Overall, the outcome of PRO-CTCAE was disregarded in the benefit assessment due to the nontransparent selection process and the inexplicable selection of items for depicting the symptomatic AEs of durvalumab.

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 at study and outcome levels – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine

Study		Outcomes									
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-BIL21, PGIS)	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[b]	Immune-related SAEs[c]	Immune-related severe AEs[c, d]	Further specific AEs[e]
TOPAZ-1	L	L	H[f]	H[f]	H[f]	H[g]	H[g]	L[h]	H[g]	H[g]	H[g]

a. Operationalized as CTCAE ≥ 3.
b. Discontinuation of 1 or more treatment components.
c. The operationalization of adverse events of special interest (AESI) is used for the global cohort for the 25/02/2022 data cutoff (see Section I 4.1).
d. Operationalized as CTCAE grade 3-4.
e. The following events were taken into account (MedDRA coding): skin and subcutaneous tissue disorders (SOC, AEs), anaemia (PT, SAEs), fever (PT, SAEs), cholangitis (PT, severe AEs).
f. Incomplete observations for potentially informative reasons (lack of follow-up 90 days after discontinuation due to progression or adverse event).
g. Incomplete observations for potentially informative reasons (lack of follow-up from 90 days after the end of treatment or with the start of subsequent anti-tumour therapy).
h. Despite the low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be restricted (see Section I 4.1).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PGIS: Patient Global Impression of Severity; PT: Preferred Term; QLQ-BIL21: Quality of Life Questionnaire – Cholangiocarcinoma and Gallbladder Cancer 21; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias is deemed low for the results on the outcome of overall survival. This concurs with the company's assessment.

The outcome-specific risk of bias for the outcomes of symptoms (symptom scales of the EORTC QLQ-C30, EORTC QLQ-BIL21, and PGIS), health status (EQ-5D VAS), and health-related quality of life (functional scales of the EORTC QLQ-C30 and EORTC QLQ-BIL21) is rated as high due to incomplete observations for potentially informative reasons because these outcomes were followed up for only 90 days in case of treatment discontinuation due to progression or AEs. For the patients included in the analysis, the return rates of the respective questionnaires decreased markedly over time in both treatment arms.

The risk of bias for the outcomes of the side effects category was rated as high. For the outcomes mentioned in the side effects category, observations are incomplete because the follow-up observation was not complete: in case of treatment discontinuation, the follow-up was implemented for only 90 days. Treatment discontinuation is therefore a potentially informative reason for the incomplete follow-up observation. The reasons for discontinuation also differed between the study arms (e.g. discontinuations due to progression: 64% versus 71%).

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "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 durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine in adult patients with unresectable or metastatic biliary carcinoma in first-line treatment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix B of the full dossier assessment. Results for common AEs can be found in I Appendix C of the full dossier assessment, and those for common immune-mediated AEs, in I Appendix D of the full dossier assessment.

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

Study **Outcome category** **Outcome**	**Durvalumab + cisplatin + gemcitabine**		**Placebo + cisplatin + gemcitabine**		**Durvalumab + cisplatin + gemcitabine versus 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]**
TOPAZ-1					
Mortality					
Overall survival	405	12.6 [11.1; 13.6] 290 (71.6)	405	10.9 [9.7; 11.7] 327 (80.7)	0.77 [0.66; 0.90] < 0.001
Morbidity					
Symptoms (EORTC QLQ-C30, first deterioration ≥ 10 points)					
Fatigue	405	1.5 [1.4; 2.1] 183 (45.2)	405	1.8 [1.4; 2.2] 188 (46.4)	1.02 [0.83; 1.26]; 0.824
Nausea and vomiting	405	2.2 [1.6; 2.8] 168 (41.5)	405	2.8 [2.1; 3.6] 164 (40.5)	1.07 [0.86; 1.32]; 0.641
Pain	405	3.6 [2.9; 4.9] 147 (36.6)	405	4.9 [3.5; 6.2] 144 (35.6)	1.11 [0.88; 1.39]; 0.378
Dyspnoea	405	4.4 [3.5; 8.7] 123 (30.4)	405	5.5 [3.5; 9.8] 121 (29.9)	1.04 [0.81; 1.34]; 0.815
Insomnia	405	5.0 [4.2; 6.7] 124 (30.6)	405	5.8 [3.7; 9.4] 121 (29.9)	1.00 [0.78; 1.29]; 0.853
Appetite loss	405	3.9 [2.9; 5.1] 142 (35.1)	405	3.5 [2.4; 5.6] 145 (35.8)	0.97 [0.77; 1.22]; 0.759
Constipation	405	4.2 [2.2; 9.2] 135 (33.3)	405	3.5 [2.5; 9.2] 139 (34.3)	0.97 [0.76; 1.23]; 0.711
Diarrhoea	405	NR 81 (20.0)	405	11.0 [9.2; NC] 84 (20.7)	0.95 [0.70; 1.29]; 0.899

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

Study Outcome category Outcome	Durvalumab + cisplatin + gemcitabine		Placebo + cisplatin + gemcitabine		Durvalumab + cisplatin + gemcitabine versus 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]
Symptoms (EORTC QLQ-BIL21, first deterioration ≥ 10 points)					
Pain[c]	405	NR 86 (21.2)	405	8.5 [6.6; NC] 92 (22.7)	0.98 [0.73; 1.32]; 0.885
Fatigue[c]	405	1.5 [1.4; 2.1] 165 (40.7)	405	2.2 [1.5; 2.9] 166 (41.0)	1.16 [0.93; 1.44]; 0.188
Jaundice[c]	405	5.6 [3.6; 7.5] 119 (29.4)	405	4.8 [3.9; 7.5] 123 (30.4)	0.98 [0.76; 1.26]; 0.913
Eating[c]	405	3.9 [2.8; 4.9] 133 (32.8)	405	5.7 [3.9; 9.2] 116 (28.6)	1.22 [0.95; 1.57]; 0.124
Side effects of treatment[c]	405	1.5 [1.4; 2.1] 173 (42.7)	405	2.3 [1.6; 2.9] 172 (42.5)	1.16 [0.93; 1.43]; 0.236
Difficulties with drainage[c]	405	NR 49 (12.1)	405	NR 31 (7.7)	1.67 [1.07; 2.65]; 0.024
PGIS (first deterioration to 5 points or 6 points)	405	NR 27 (6.7)	405	NR 19 (4.7)	1.38 [0.77; 2.51]; 0.316
Health status (EQ-5D VAS, first deterioration by ≥ 15 points)	405	8.8 [5.6; NC] 104 (25.7)	405	7.7 [5.8; 10.2] 109 (26.9)	0.90 [0.69; 1.18]; 0.421
Health-related quality of life					
EORTC QLQ-C30 (first deterioration ≥ 10 points)					
Global health status	405	4.3 [2.8; 6.3] 145 (35.8)	405	4.2 [2.4; 6.7] 145 (35.8)	0.96 [0.76; 1.21]; 0.746
Physical functioning	405	3.5 [2.8; 6.5] 141 (34.8)	405	4.2 [3.2; 6.5] 138 (34.1)	1.02 [0.80; 1.29]; 0.839
Role functioning	405	2.2 [2.1; 2.9] 166 (41.0)	405	2.6 [2.1; 3.5] 171 (42.2)	1.03 [0.83; 1.28]; 0.740
Emotional functioning	405	12.2 [5.8; NC] 100 (24.7)	405	6.8 [4.3; NC] 111 (27.4)	0.85 [0.65; 1.11]; 0.228
Cognitive functioning	405	3.0 [2.8; 3.6] 158 (39.0)	405	3.8 [2.8; 5.4] 142 (35.1)	1.12 [0.89; 1.41]; 0.283
Social functioning	405	3.1 [2.1; 4.5] 152 (37.5)	405	3.7 [2.7; 5.6] 142 (35.1)	1.08 [0.86; 1.35]; 0.450

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

Study **Outcome category** **Outcome**	**Durvalumab + cisplatin + gemcitabine**		**Placebo + cisplatin + gemcitabine**		**Durvalumab + cisplatin + gemcitabine versus 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]**
EORTC QLQ-BIL21 (first deterioration ≥ 10 points)					
Anxiety	405	11.1 [6.7; NC] 91 (22.5)	405	NR 92 (22.7)	0.96 [0.71; 1.28]; 0.670
Concern about weight loss	405	9.3 [6.3; NC] 97 (24.0)	405	17.5 [9.2; NC] 85 (21.0)	1.22 [0.91; 1.64]; 0.185

a. Effect and CI: Stratified Cox proportional hazards model adjusted by disease status and primary tumour location.
b. Stratified log rank test adjusted by disease status and primary tumour location.
c. In departure from the company's approach, this scale was assigned to the symptoms category rather than the health-related quality of life category.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached; QLQ-BIL21: Quality of Life Questionnaire – Cholangiocarcinoma and Gallbladder Cancer 21; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial

Table 16: Results (side effects) – RCT, direct comparison: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine

Study Outcome category Outcome	Durvalumab + cisplatin + gemcitabine		Placebo + cisplatin + gemcitabine		Durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
TOPAZ-1					
Side effects					
AEs (supplementary information)	402	399 (99.3)	403	399 (99.0)	–
SAEs	402	190 (47.3)	403	171 (42.4)	1.11 [0.96; 1.30]; 0.212
Severe AEs[c]	402	313 (77.9)	403	315 (78.2)	0.98 [0.70; 1.39]; 0.956
Discontinuation due to AEs	402	56 (13.9)	403	57 (14.1)	1.00 [0.93; 1.07]; 0.948
Immune-related SAEs[d]	338	13 (3.8)	342	10 (2.9)	1.32 [0.58; 2.96]; 0.533
Immune-related severe AEs[d,e]	338	13 (3.8)	342	10 (2.9)	1.32 [0.58; 2.96]; 0.533
Skin and subcutaneous tissue disorders (SOC, AEs)	402	158 (39.3)	403	102 (25.3)	1.55 [1.26; 1.91]; < 0.001
Fever (PT, SAE)	402	18 (3.7)	403	8 (2.0)	2.26 [0.99; 5.13][f]; 0.048[f]
Anaemia (PT, SAEs)	402	14 (3.5)	403	5 (1.2)	2.81 [1.02; 7.72]; 0.039
Cholangitis (PT, severe AEs[c])	402	23 (5.7)	403	11 (2.7)	2.10 [1.04; 4.24]; 0.039

a. Institute's calculation of effect and CI (asymptotic).
b. Institute's calculation, unconditional exact test, CSZ method according to [17].
c. Operationalized as CTCAE grade ≥ 3.
d. Global cohort on the 25/02/2022 data cutoff.
e. Operationalized as CTCAE grade 3 to 4.
f. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

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; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

The available information allows deriving no more than an indication, e.g. of an added benefit, for the outcome of overall survival. Therefore, at most hints, e.g. of an added benefit, can be derived for all other outcomes.

Mortality

Overall survival

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

Morbidity

Symptoms

EORTC QLQ-C30

Symptom scales

No statistically significant difference between treatment groups was found for any of the EORTC QLQ-C30 symptom scales. This results in no hint of an added benefit of durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

EORTC QLQ-BIL21

Difficulties with drainage

For the outcome of difficulties with drainage, there was a statistically significant difference between treatment groups to the disadvantage of durvalumab + cisplatin + gemcitabine. For this outcome of the non-serious/non-severe symptoms / late complications 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 durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; an added benefit is therefore not proven.

Pain, fatigue, jaundice, difficulty eating, and side effects of treatment

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

PGIS

There was no statistically significant difference between the treatment groups for the outcome of PGIS. This results in no hint of an added benefit of durvalumab + cisplatin +

gemcitabine in comparison with cisplatin + gemcitabine; an added benefit is therefore not proven.

Health status

The outcome of health status was surveyed by EQ-5D VAS.

No statistically significant differences between treatment groups were found for the outcome of health status. This results in no hint of an added benefit of durvalumab + 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 shown for the health-related quality of life outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-BIL21. This results in no hint of an added benefit of durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine for any of them; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation 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 durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; greater or lesser harm is therefore not proven.

Immune-related SAEs and immune-related severe AEs (CTCAE grade 3-4)

No statistically significant difference between the treatment groups was shown for either of the outcomes of immune-related SAEs or immune-related severe AEs (CTCAE grade 3 to 4). In each case, this results in no hint of greater or lesser harm from durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine; greater or lesser harm is therefore not proven.

Specific AEs

Diseases of the skin and subcutaneous tissue (AEs), fever (AEs), anaemia (AEs) and cholangitis (severe AEs)

For each of the outcomes of skin and subcutaneous tissue disorders (AEs), fever (SAEs), anaemia (SAEs), and cholangitis (severe AEs), a statistically significant difference was found to the disadvantage of durvalumab + cisplatin + gemcitabine in comparison with placebo + cisplatin + gemcitabine. In each case, this results in a hint of greater harm from durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)
- stage of disease (locally advanced versus metastasized)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only the results showing 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 1 subgroup.

Using the methods described, no relevant effect modification by the subgroup characteristics of age or metastases at baseline was identified for the analysed outcomes.

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 *General Methods* of IQWiG [18].

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 the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4.3 (see Table 17).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier whether the following symptom outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Symptoms (EORTC QLQ-BIL21)

Difficulties with drainage

For the outcome of difficulties with drainage, the available severity data are insufficient for a classification as serious/severe. The outcome of difficulties with drainage was therefore assigned to the outcome category of non-serious/non-severe symptoms.

Table 17: Extent of added benefit at outcome level: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier**	**Durvalumab + cisplatin + gemcitabine versus 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	12.6 months vs. 11.5 months HR: 0.77 [0.66; 0.90]; p < 0.001 Probability: indication	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit; extent: considerable
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, first deterioration ≥ 10 points)		
Fatigue	1.5 vs. 1.8 HR: 1.02 [0.83; 1.26]; p = 0.824	Lesser/Added benefit not proven
Nausea and vomiting	2.2 vs. 2.8 HR: 1.07 [0.86; 1.32]; p = 0.641	Lesser/Added benefit not proven
Pain	3.6 vs. 4.9 HR: 1.11 [0.88; 1.39]; p = 0.378	Lesser/Added benefit not proven
Dyspnoea	4.4 vs. 5.5 HR: 1.04 [0.81; 1.34]; p = 0.815	Lesser/Added benefit not proven
Insomnia	5.0 vs. 5.8 HR: 1.00 [0.78; 1.29]; p = 0.853	Lesser/Added benefit not proven
Appetite loss	3.9 vs. 3.5 HR: 0.97 [0.77; 1.22]; p = 0.759	Lesser/Added benefit not proven
Constipation	4.2 vs. 3.5 HR: 0.97 [0.76; 1.23]; p = 0.711	Lesser/Added benefit not proven
Diarrhoea	NR vs. 11.0 HR: 0.95 [0.70; 1.29]; p = 0.899	Lesser/Added benefit not proven

Table 17: Extent of added benefit at outcome level: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier**	**Durvalumab + cisplatin + gemcitabine versus 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, first deterioration ≥ 10 points)		
Pain	NR vs. 8.5 HR: 0.98 [0.73; 1.32]; p = 0.885	Lesser/Added benefit not proven
Fatigue	1.5 vs. 2.2 HR: 1.16 [0.93; 1.44]; p = 0.188	Lesser/Added benefit not proven
Jaundice	5.6 vs. 4.8 HR: 0.98 [0.76; 1.26]; p = 0.913	Lesser/Added benefit not proven
Eating	3.9 vs. 5.7 HR: 1.22 [0.95; 1.57]; p = 0.124	Lesser/Added benefit not proven
Side effects of treatment	1.5 vs. 2.3 HR: 1.16 [0.93; 1.43]; p = 0.236	Lesser/Added benefit not proven
Difficulties with drainage	NR vs. NR HR: 1.67 [1.07; 2.65]; HR: 0.60 [0.39; 0.93][d] p = 0.024	Outcome category: non-serious/non-severe side effects $0.90 < CI_u \leq 1.00$ Lesser/Added benefit not proven
PGIS (first deterioration to 5 points or 6 points)	NR vs. NR HR: 1.38 [0.77; 2.51]; p = 0.316	Lesser/Added benefit not proven
Health status (EQ-5D-VAS, first deterioration by ≥ 15 points)	8.8 vs. 7.7 HR: 0.90 [0.69; 1.18]; p = 0.421	Lesser/Added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (first deterioration ≥ 10 points)		
Global health status	4.3 vs. 4.2 HR: 0.96 [0.76; 1.21]; p = 0.746	Lesser/Added benefit not proven
Physical functioning	3.5 vs. 4.2 HR: 1.02 [0.80; 1.29]; p = 0.839	Lesser/Added benefit not proven

Table 17: Extent of added benefit at outcome level: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier**	**Durvalumab + cisplatin + gemcitabine versus 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	2.2 vs. 2.6 HR: 1.03 [0.83; 1.28]; p = 0.740	Lesser/Added benefit not proven
Emotional functioning	12.2 vs. 6.8 HR: 0.85 [0.65; 1.11]; p = 0.228	Lesser/Added benefit not proven
Cognitive functioning	3.0 vs. 3.8 HR: 1.12 [0.89; 1.41]; p = 0.283	Lesser/Added benefit not proven
Social functioning	3.1 vs. 3.7 HR: 1.08 [0.86; 1.35]; p = 0.450	Lesser/Added benefit not proven
EORTC QLQ-BIL21 (first deterioration ≥ 10 points)		
Anxiety	11.1 vs. NR HR: 0.96 [0.71; 1.28]; p = 0.670	Lesser/Added benefit not proven
Concern about weight loss	9.3 vs. 17.5 HR: 1.22 [0.91; 1.64]; p = 0.185	Lesser/Added benefit not proven
Side effects		
SAEs	47.3% vs. 42.4% RR: 1.11 [0.96; 1.30]; p = 0.212	Greater/Lesser harm not proven
Severe AEs	77.9% vs. 78.2% RR: 0.98 [0.70; 1.39]; p = 0.956	Greater/Lesser harm not proven
Discontinuation due to AEs	13.9% vs. 14.1% RR: 1.00 [0.93; 1.07]; p = 0.948	Greater/Lesser harm not proven
Immune-related SAEs[c]	3.8% vs. 2.9% RR: 1.32 [0.58; 2.96]; p = 0.533	Greater/Lesser harm not proven
Immune-related severe AEs[c]	3.8% vs. 2.9% RR: 1.32 [0.58; 2.96]; p = 0.533	Greater/Lesser harm not proven

Table 17: Extent of added benefit at outcome level: durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine (multipage table)

Outcome category **Outcome** **Effect modifier**	**Durvalumab + cisplatin + gemcitabine versus placebo + cisplatin + gemcitabine** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Skin and subcutaneous tissue disorders (AEs)	39.3% vs. 25.3% RR: 1.55 [1.26; 1.91]; RR: 0.65 [0.52; 0.79][d] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Fever (SAE)	4.5% vs. 2.0% RR: 2.26 [0.99; 5.13]; RR: 0.44 [0.19; 1.01][d] p = 0.048 Probability: hint	Outcome category: serious/severe side effects Greater harm[f]; extent: minor[g]
Anaemia (SAEs)	3.5% vs. 1.2% RR: 2.81 [1.02; 7.72] RR: 0.36 [0.13; 0.98][d] p = 0.039 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: minor
Cholangitis (severe AEs)	5.7% vs. 2.7% RR: 2.10 [1.04; 4.24] RR: 0.48 [0.24; 0.96][d] p = 0.039 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor

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. Global cohort at 25/02/2022 data cut-off.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The result of the statistical test is decisive for the derivation of the added benefit.
f. 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; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NR: not reached; QLQ-BIL21: Quality of Life Questionnaire – Cholangiocarcinoma and Gallbladder Cancer 21; QLQ-C30: Quality of Life Questionnaire – Core 30; 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 durvalumab + cisplatin + gemcitabine versus cisplatin + gemcitabine

Favourable effects	**Unfavourable effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: indication of an added benefit – extent: considerable	–
Outcomes with shortened observation period	
–	Serious/Severe side effects: ▪ Fever (SAE): hint of greater harm – extent: minor ▪ Anaemia (SAE): hint of greater harm – extent: minor ▪ Cholangitis (severe AEs): hint of greater harm – extent: minor
–	Non-serious/non-severe side effects: ▪ Skin and subcutaneous tissue disorders (AEs): hint of greater harm – extent: considerable
AE: adverse event; SAE: serious adverse event	

Overall, both favourable and unfavourable effects of durvalumab + cisplatin + gemcitabine were found in comparison with the ACT.

For the favourable effects, there was an indication of major added benefit for the outcome of overall survival. For the unfavourable effects, the specific AEs of fever (AE), anaemia (SAE), cholangitis (severe AE), and skin and subcutaneous tissue disorders (AEs) each show a hint of minor or considerable harm.

In summary, there is an indication of considerable added benefit for adult patients with unresectable or metastatic biliary carcinoma in first-line therapy compared with the ACT of cisplatin in combination with gemcitabine.

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

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adults with unresectable or metastatic biliary tract cancer in combination with gemcitabine and cisplatin[b]	Cisplatin in combination with gemcitabine, see Section K of the Pharmaceutical Directive, Annex VI.	Indication of considerable added benefit

a. Presented is the respective ACT specified by the G-BA.
b. In light of the therapy carried out in the intervention arm, patients are presumably eligible for intensive combination chemotherapy with regard to their general condition and potential comorbidities.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above concurs with that of the company.

The approach for deriving 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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