Durvalumab (biliary tract cancer)

Addendum to Project A23-26 (dossier assessment)[1]

ADDENDUM

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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

IQWiG employees involved in the addendum

- Kai Lucaßen
- Ana Liberman
- Katrin Nink
- Christoph Schürmann

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AESI	adverse event of special interest
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SMQ	standardized MedDRA query

1 Background

On 9 August 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-26 (Durvalumab – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the following analyses presented by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure [2], taking into account the information provided in the dossier [3]:

- separate analyses of the China expansion cohort and the global cohort for the overall survival outcome
- analyses of adverse events of special interest (AESIs) for the pooled cohort without consideration of standardized MedDRA queries (SMQs)

In addition, an appraisal was requested regarding the English-language appendix to the study report on the China extension cohort, which was submitted by the company in the commenting procedure.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The benefit assessment of durvalumab + cisplatin + gemcitabine [1] used the TOPAZ-1 study, in which durvalumab + cisplatin + gemcitabine was compared to placebo + cisplatin + gemcitabine in the first-line therapy of adults with unresectable or metastatic biliary tract cancer. The pooled analysis based on individual patient data of the global cohort and the China expansion cohort was used as the relevant study population. Patients from study centres around the world were included in the global cohort. According to the company, the separate recruitment of the China expansion cohort was conducted for the purpose of obtaining a marketing authorization for durvalumab in China. Virtually identical study protocols and statistical analysis plans (SAPs) were used for the patients in the China expansion cohort and the global cohort.

2.1 Analyses of the China expansion cohort and the global cohort for the outcome of overall survival

For the outcome of overall survival, the benefit assessment was based on the pooled population of the TOPAZ-1 study. In its comments [2], the company has submitted separate analyses of the global cohort (25 February 2022 data cutoff) and the China expansion cohort (14 October 2022 data cutoff). For the benefit assessment, the results of the pooled cohort presented in the dossier assessment are still relevant.

Table 1 shows the overall survival results separately for the global cohort and the China expansion cohort. Where necessary, calculations conducted by the Institute are provided in addition to the data provided by the company.

Table 1: Results (mortality) – RCT, direct comparison: durvalumab + chemotherapy versus placebo + chemotherapy

Study Outcome category Outcome	Durvalumab + cisplatin + gemcitabine		Placebo + cisplatin + gemcitabine		Durvalumab + 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
TOPAZ-1					
Mortality					
Overall survival					
Global cohort[b]	341	12.9 [11.6; 14.1] 248 (72.7)	344	11.3 [10.1; 12.5] 279 (81.1)	0.76 [0.64; 0.91]; 0.002[c]
China expansion cohort[d]	65	9.1 [6.3; 13.7] 43 (66.2)	65	9.2 [7.1; 10.2] 51 (78.5)	0.78 [0.51; 1.18]; 0.238

a. Effect and CI: stratified Cox proportional hazard model adjusted for disease status and primary tumour location.
b. 25 February 2022 data cutoff.
c. Institute's calculation from data on the CI.
d. 14 October 2022 data cutoff.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial

For the outcome of overall survival, the global cohort shows a statistically significant difference in favour of durvalumab + cisplatin + gemcitabine in comparison with cisplatin + gemcitabine. In the China expansion cohort, there was no statistically significant difference between the treatment groups. The subsequently submitted results of the individual cohorts are consistent with each other, both in terms of the direction of the effect and the position of the point estimates.

2.2 Analyses of the AESIs for the pooled cohort without inclusion of SMQs

In the benefit assessment, the AESIs prespecified in the TOPAZ-1 study were used for drawing conclusions on immune-mediated adverse events (AEs). For the AESI in the pooled cohort, however, the only available results failed to comply with the predefined list by also including the additional SMQs of hepatic disorders, biliary disorders, and haematopoietic cytopenias. As described in the dossier assessment, these SMQs partly reflect symptoms of the underlying disease and side effects of chemotherapy but are irrelevant for the assessment of immune-mediated AEs. The benefit assessment therefore used the analyses of AESIs in the global cohort at the 25 February 2022 data cutoff for immune-mediated AEs; they exclude the SMQs

mentioned above as prespecified in the study protocol. In its comments, the company subsequently submitted AESI analyses without SMQs for the pooled cohort. These analyses are used in this assessment for drawing conclusions on immune-mediated AEs.

Table 2 summarizes the AESI results for the pooled cohort without SMQs. Where necessary, calculations conducted by the Institute are provided in addition to the data presented by the company.

Table 2: 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 vs. placebo + cisplatin + gemcitabine
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
TOPAZ-1					
Side effects					
Immune-mediated SAEs[c]	402	15 (3.7)	403	14 (3.5)	1.07 [0.57; 2.20]; 0.902
Immune-mediated severe AEs[c, d]	402	15 (3.7)	403	14 (3.5)	1.07 [0.57; 2.20]; 0.902

a. Institute's calculation of effect and CI (asymptotic).
b. Institute's calculation, unconditional exact test, CSZ method according to [4].
c. Pooled analysis excluding SMQs: data cutoffs from 14 October 2022 (China expansion cohort) and 25 February 2022 (global cohort)
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; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: standardized MedDRA query; SOC: System Organ Class

No statistically significant difference between the treatment groups was shown for the outcomes of immune-mediated severe adverse events (SAEs) and immune-mediated severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). 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.

2.3 Subsequently submitted study documents for the China expansion cohort

The company's dossier presents on the basis of patient-specific data a pooled analysis of 2 cohorts: the global cohort, and the China extension cohort. This pooled cohort was deemed relevant and used for the assessment. The company's dossier presents a study report for the global cohort. The study report for the China expansion cohort is not available in the dossier.

The available information fails to clarify whether a study report for the China extension cohort at the 14 October 2022 data cutoff was already available at the time of dossier submission. Together with its comments, the company subsequently submitted data for the China expansion cohort [2].

In its comments, the company firstly compares the results on overall survival (hazard ratio [HR], confidence interval [CI], and p-value) of the China expansion cohort versus the global cohort and the pooled cohort. These are discussed in Section 2.1. Secondly, the company has submitted a separate document which it refers to as an appendix to the study report. This presumably represents Section 14 of the study report (the contained analyses are dated 16 December 2022), which is structured in accordance with the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E3. As per Guideline ICH E3 [5], Section 14 presents tables, figures, and diagrams which are referenced but not included in the text of the study report. The company does not present any further parts of the study report or separate analyses. Irrespective of this, the relevant data of the China expansion cohort are already included in the pooled cohort used in dossier assessment A23-26 and were included in the assessment of added benefit.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of durvalumab + cisplatin + gemcitabine from dossier assessment A23-26.

Table 3 below shows the result of the benefit assessment of durvalumab + cisplatin + gemcitabine, taking into account dossier assessment A23-26 and the present addendum.

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
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 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. Against the background of 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. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

3 References

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