IQWiG Reports – Commission No. A18-88

Atezolizumab (urothelial carcinoma first-line treatment) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Atezolizumab (Urothelkarzinom Erstlinientherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 March 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IDMC	Independent Data Monitoring Committee
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V (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 atezolizumab. The pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier on the drug to be evaluated as monotherapy in the first-line treatment of locally advanced or metastatic urothelial carcinoma in the originally approved therapeutic indication on 29 September 2017 for the early benefit assessment. On 2 August 2018, the G-BA requested a new benefit assessment because of new scientific findings. This was based on the decision of the European Commission of 2 July 2018 on a restriction in the approval, because an ongoing clinical study on atezolizumab showed reduced survival in the first-line treatment of the urothelial carcinoma in adults with low programmed cell death ligand 1 (PD-L1) expression. The benefit assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 19 December 2018.

Research question

The aim of this report was to assess the added benefit of atezolizumab in comparison with chemotherapy specified by the physician as appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing first-line treatment is unsuitable and whose tumours have a PD-L1 expression ≥ 5%.

For the benefit assessment of atezolizumab, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of atezolizumab

Subindication	**ACT[a]**
Adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable and whose tumours have a PD-L1 expression ≥ 5%	Chemotherapy specified by the physician
a: Presentation of the ACT specified by the G-BA. G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

As in the dossier on the originally approved therapeutic indication of the first-line treatment, the company specified carboplatin + gemcitabine as the only relevant comparator therapy for the present research question. The company's choice of the ACT has no effect on the present benefit assessment, because the presented data are not suitable for the assessment of an added benefit of atezolizumab.

Assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

As already done in the dossier of 25 September 2017, the company presented a comparison of individual arms from different studies in its current dossier. The data largely correspond to those the company had already presented in its dossier on the originally approved therapeutic indication. However, as described in the first assessment (A17-51), these data are incomplete particularly with regard to the AEs and the effects are still insufficiently large to rule out that the differences were merely based on the impact of confounding variables. The data are still unsuitable to derive an added benefit of atezolizumab in comparison with the ACT in the therapeutic indication to be assessed. The preliminary results of the ongoing randomized controlled trial (RCT) IMvigor130, which resulted in the restriction in the approval, support this assessment. Informative results of this RCT on all patient-relevant outcomes must be awaited for the benefit assessment.

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

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

Table 3 presents a summary of the probability and extent of the added benefit of atezolizumab.

Table 3: Atezolizumab – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable and whose tumours have a PD-L1 expression ≥ 5%.	Chemotherapy specified by the physician	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of atezolizumab in comparison with chemotherapy specified by the physician as ACT in adult patients with locally advanced or

[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].

metastatic urothelial carcinoma for whom cisplatin-containing first-line treatment is unsuitable and whose tumours have a PD-L1 expression ≥ 5%.

For the benefit assessment of atezolizumab, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of atezolizumab

Subindication	**ACT[a]**
Adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable and whose tumours have a PD-L1 expression ≥ 5%.	Chemotherapy specified by the physician
a: Presentation of the ACT specified by the G-BA. G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

As in the dossier on the originally approved therapeutic indication of the first-line treatment [3] (corresponding dossier assessment A17-51 [4]), the company specified carboplatin + gemcitabine as the only relevant comparator therapy for the present research question. The company's choice of the ACT has no effect on the present benefit assessment, because the presented data are not suitable for the assessment of an added benefit of atezolizumab (see Section 2.3).

Assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 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 lists on atezolizumab (status: 23 October 2018)
- bibliographical literature search on atezolizumab (last search on 10 October 2018)
- search in trial registries for studies on atezolizumab (last search on 23 October 2018)
- bibliographical literature search on the ACT (last search on 10 October 2018)
- search in trial registries for studies on the ACT (last search on 22 October 2018)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 18 January 2019)

The check of the completeness of the study pool produced no suitable data for the assessment of the added benefit of atezolizumab for the present research question.

The company presented a comparison of individual arms from different studies. However, this comparison was unsuitable to derive an added benefit of atezolizumab in comparison with the ACT. This is explained below.

Study pool of the company

As in the dossier on the originally approved therapeutic indication, the company presented no results from RCTs of direct comparison on the comparison of atezolizumab with the ACT. In its study list, the company cited an RCT in the current therapeutic indication, but excluded this RCT due to the lack of a result report (see below: information on the IMvigor130 study). Since the company also identified no suitable studies for an indirect comparison, it presented a comparison of individual arms from different studies instead.

As in the dossier on the originally approved therapeutic indication, the company used cohort 1 of the IMvigor210 study [11] on the atezolizumab side, and the single-arm prospective studies Bamias 2007 [5], Bellmunt 2001 [6], Carles 2000 [7] and Linardou 2004 [8] as well as one arm from the RCT De Santis 2012 [9] on the carboplatin + gemcitabine side for the derivation of an added benefit. The company excluded retrospective clinical studies in its information retrieval for studies on the first-line treatment with carboplatin + gemcitabine.

The characteristics of the studies once more included by the company in its current dossier are found in Appendix A of the first assessment A17-51 [4]. As in the dossier on the first assessment, the comparison of individual arms from different studies presented by the company was based on the total populations of the studies in accordance with the originally approved therapeutic indication. Among other things, the company justified this with the explanation that all and every study available for the comparison of carboplatin + gemcitabine had been conducted before the availability of the PD-L1 test. Moreover, the company explained that it still considered the total population of the IMvigor210 study to be the adequate basis for the comparison, because the PD-L1 status had no systematic impact on the results in the IMvigor210 study. For the IMvigor210 study, the company provided a descriptive presentation of the data of the population in accordance with the restriction in the approval. 32 of the 123 patients included in the study (about 26% of the total population) had a tumour with a PD-L1 expression ≥ 5%.

Assessment of the evidence presented by the company

Lack of suitability of the data presented by the company for the derivation of an added benefit

The data used by the company for the derivation of an added benefit in its current dossier still correspond to those it had already presented in its dossier on the originally approved therapeutic indication. One difference is that a more recent data cut-off was analysed for the single-arm study with atezolizumab (IMvigor210). According to the new data cut-off in the IMvigor210 study, median survival in the total population was marginally longer (0.4 months) than it was after the data cut-off available for the first assessment. Median survival time in the IMvigor210

study is 4 months shorter in the population according to the current approval (patients with a PD-L1 expression ≥ 5%) than in the total population. As in dossier assessment A17-51 [4], the data situation on the AEs is incomplete, because comparator data are missing for some AEs.

As the comparison presented by the company corresponds to the one it had already submitted in its dossier on the benefit assessment in the original therapeutic indication, the related detailed assessment can be found in the first assessment of atezolizumab [3]. As described there, conclusions on the added benefit based on a comparison of individual arms from different studies can only be drawn in the presence of very large effects due to the high uncertainty of results. However, there were still no such effects for the relevant outcomes on overall survival, symptoms, health-related quality of life, as well as overall rates of AEs, SAEs, discontinuation due to AEs, and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). Moreover, the incomplete data situation on the AEs allowed no adequate comparison between atezolizumab and carboplatin + gemcitabine.

Altogether, the data situation has remained insufficient for the derivation of an added benefit of atezolizumab, particularly for the population according to the restricted approval.

New findings from an RCT in the therapeutic indication support the assessment on the lack of suitability of the data presented by the company

The RCT that resulted in the restriction in the approval was the ongoing partially blinded 3-arm parallel group study IMvigor130 [10,11]. This study compared atezolizumab in combination with platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin) (arm A) with atezolizumab monotherapy (arm B) and placebo in combination with platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin) (arm C). Treatment-naive adult patients with locally advanced or metastatic urothelial carcinoma were enrolled in the study. Among other things, randomization was stratified according to the decision on whether cisplatin-based chemotherapy was suitable for the patients made by the investigator prior to randomization.3

The therapeutic indication was restricted after preliminary data from this ongoing RCT showed reduced survival in patients with low PD-L1 expression for atezolizumab as monotherapy in comparison with platinum-based chemotherapy. The analysed data were snapshot data of an unplanned interim analysis that had been evaluated by the Independent Data Monitoring Committee (IDMC) within the framework of the regular reviews [12]. Regular analyses have not been conducted for this study to date. According to the ClinicalTrials.gov registry, first analyses of the IMvigor130 study are planned for November 2020 [13].

The company cited these RCTs and noted that no result report was available. It did not further address this study and the interim results because of which the restriction of approval was made. The study protocol is contained in Module 5.

The preliminary results from the ongoing IMvigor130 study, which resulted in the restriction in the approval, support the assessment on the lack of suitability of the data presented by the company for the derivation of an added benefit. Informative results of the above RCT on all patient-relevant outcomes must be awaited for the benefit assessment.

Summary

The data used by the company for the derivation of an added benefit in its current dossier still correspond to those it had already presented in its dossier on the originally approved therapeutic indication. The data are unsuitable to derive an added benefit of atezolizumab in comparison with the ACT in the therapeutic indication to be assessed. The data of the ongoing RCT IMvigor130 support this assessment.

2.4 Results on added benefit

The company presented no suitable data for the assessment of atezolizumab in the treatment of locally advanced or metastatic urothelial carcinoma in adults for whom cisplatin-containing first-line treatment is unsuitable and whose tumours have a PD-L1 expression ≥ 5%. This resulted in no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of atezolizumab in comparison with the ACT.

Table 5: Atezolizumab – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable and whose tumours have a PD-L1 expression ≥ 5%	Chemotherapy specified by the physician	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. Federal Joint Committee; PD-L1: programmed cell death ligand 1		

This assessment deviates from that of the company, which derived a hint of a non-quantifiable added benefit on the basis of the provided data.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

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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