IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-51

Atezolizumab (urothelial carcinoma, first-line treatment) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *(Urothelkarzinom Erstlinientherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2017). 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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[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
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
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)
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PS	Performance Status
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 29 September 2017.

Research question

The aim of this report was to assess the added benefit of atezolizumab compared with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing first-line treatment is unsuitable.

Table 2: Research questions of the benefit assessment of atezolizumab

Therapeutic indication	**ACT[a]**
Adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable (first-line treatment)	Chemotherapy specified by the physician
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company chose a combination therapy of carboplatin and gemcitabine (hereinafter referred to as "carboplatin + gemcitabine") as ACT.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

The company identified no randomized controlled trials (RCTs) of direct comparison on the comparison of atezolizumab versus the ACT. Since the company also identified no suitable studies for an indirect comparison, it presented a comparison of individual arms from different studies instead.

The company identified 6 studies and used one arm from each of these studies for the benefit assessment. The company used cohort 1 of the IMvigor210 study for atezolizumab and compared it with the single-arm prospective studies Bamias 2007, Bellmunt 2001, Carles 2000 and Linardou 2004, as well as with one arm from the RCT De Santis 2012. The company excluded retrospective clinical studies in its search for studies on the first-line treatment with carboplatin + gemcitabine.

All studies investigated patients for whom cisplatin-based treatment is unsuitable according to the inclusion criteria of the studies. Unsuitability for cisplatin was determined based on the presence of at least one of the following criteria according to Galsky 2011: Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥ 2 or Karnofsky performance score of 60% to 70%, reduced renal function, hearing loss (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 2), peripheral neuropathy (CTCAE grade ≥ 2) or New York Heart Association [NYHA] class III heart failure. Publications defining patients as unsuitable for cisplatin-based chemotherapy could also be included.

The data presented by the company were unsuitable to derive an added benefit of atezolizumab in comparison with the ACT. This is justified below.

Data situation

Differences between atezolizumab and carboplatin + gemcitabine in overall survival not large enough

The certainty of results was low due to the comparison of individual arms of different studies conducted by the company. The effect sizes shown by the company on overall survival were not large enough not to be explicable only by confounding factors. A conclusion on the added benefit for the outcome "overall survival" is therefore not possible on the basis of the results presented.

Incomplete data and differences between atezolizumab and carboplatin + gemcitabine in overall rates of adverse events not large enough

The company's dossier contained overall rates of adverse events (AEs), serious AEs (SAEs), and severe AEs (CTCAE grade ≥ 3) only for the IMvigor210 study. These outcomes were not reported in the comparator studies. The overall rates of AEs leading to discontinuation of the treatment were reported in only 2 of the 5 comparator studies. Based on these data, the company derived a minor added benefit of atezolizumab for the outcome "discontinuation due to AEs". The difference between the treatments was not large enough not to be explicable only by confounding factors, however. Hence the data on the overall rates of side effects were overall unsuitable to draw a conclusion on the added benefit of atezolizumab.

Incomplete data on the comparison of individual outcomes on specific adverse events

The data presented by the company showed lesser harm of atezolizumab for individual specific AE outcomes with an effect size that cannot be explained only by confounding factors. However, the choice of AEs in the present comparison was restricted to AEs presented in at least one of the comparator studies that only investigated chemotherapies. The haematologic toxicities identified by the company are characteristic and common class effects of chemotherapeutic agents such as carboplatin. In contrast, AEs characteristic of immunotherapeutic agents such as atezolizumab were not reported in the comparator studies. In its dossier, the company described the IMvigor210 study data on AEs associated with immunotherapy, but did not put them into a context allowing an estimation of the extent of

the observed AEs in the present therapeutic indication. Furthermore, the operationalization of immune-related AEs in the IMvigor210 study was based on a list of prespecified AEs and was therefore unsuitable to record all immune-related AEs of the IMvigor210 study.

The data and the company's consideration on specific side effects were therefore incomplete and allowed no comprehensive comparison of the side effects of atezolizumab versus carboplatin + gemcitabine.

Restriction of the appropriate comparator therapy

The company chose carboplatin + gemcitabine as comparator therapy because it considered this therapy to concur with the regular treatment specified by a physician on the basis of rational decision criteria and current guideline recommendations.

This assessment was not shared for all patients. The German S3 guideline explicitly states that there is no standard therapy for patients for whom cisplatin-containing treatment is unsuitable because of the heterogeneity of this patient population. For patients with an ECOG PS of 0 or 1, the guideline recommends treatment with carboplatin + gemcitabine although this treatment is not approved for this therapeutic indication. Patients with an ECOG PS of 2 or higher can be treated with monochemotherapy, according to the guideline. Particularly patients with an unfavourable risk profile (ECOG PS ≥ 2 and reduced renal function or Bajorin risk group 2) have only little benefit from carboplatin-based combination therapy. It should be noted that each of the studies included by the company for the main analysis included a relevant proportion of patients with ECOG PS ≥ 2 or Karnofsky performance score ≤ 70% (19–68%). In addition, all studies used reduced renal function as a criterion for unsuitability for cisplatin-containing therapy. It was therefore unclear to what extent carboplatin + gemcitabine concurred with the treatment specified by the physician for all patients considered. Hence as a result of the company's restriction of the comparator therapy to only carboplatin + gemcitabine, the ACT defined by the G-BA – chemotherapy specified by the physician – was not completely represented.

Summary

In summary, the incomplete data situation allowed no adequate comparison between atezolizumab and carboplatin + gemcitabine. In addition, conclusions on the added benefit based on a comparison of individual arms of different studies can only be drawn in the presence of very large effects due to the high uncertainty of results. There were 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 (CTCAE grade ≥ 3) AEs.

As a result of the company's restriction of the comparator therapy to only carboplatin + gemcitabine, the ACT defined by the G-BA – chemotherapy specified by the physician – was not completely represented.

Overall, no usable data were available for the assessment of atezolizumab in adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing first-line treatment is unsuitable.

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 probability and extent of the added benefit of atezolizumab.

Table 3: Atezolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable (first-line treatment)	Chemotherapy specified by the physician	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. 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 compared with the ACT in adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing first-line treatment is unsuitable.

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

[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].

Table 4: Research questions of the benefit assessment of atezolizumab

Therapeutic indication	**ACT[a]**
Adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable (first-line treatment)	Chemotherapy specified by the physician
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company chose a combination therapy of carboplatin and gemcitabine (hereinafter referred to as "carboplatin + gemcitabine") as ACT. This approach was not followed (see Section 2.3 and Section 2.7.1 of the full dossier assessment).

The 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: 27 July 2017)
- bibliographical literature search on atezolizumab (last search on 5 July 2017)
- search in trial registries for studies on atezolizumab (last search on 13 July 2017)
- bibliographical literature search on the ACT (last search on 5 July 2017)
- search in trial registries for studies on the ACT (last search on 12 July 2017)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 4 October 2017)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of atezolizumab versus the ACT specified by the G-BA in adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing first-line treatment is unsuitable.

The comparison of individual arms from different studies presented by the company was unsuitable to derive an added benefit of atezolizumab in comparison with the ACT. This is justified below.

Study pool of the company

The company identified no RCTs of direct comparison on the comparison of atezolizumab versus the ACT. Since the company also identified no suitable studies for an indirect comparison, it presented a comparison of individual arms from different studies instead.

In its main analysis, the company compared cohort 1 of the IMvigor210 study [3] with the single-arm prospective studies Bamias 2007 [4], Bellmunt 2001 [5], Carles 2000 [6] and Linardou 2004 [7], as well as with one arm from the RCT De Santis 2012 [8]. The company excluded retrospective clinical studies in its search for studies on the first-line treatment with carboplatin + gemcitabine.

In its main analysis, the company considered studies in the therapeutic indication of atezolizumab with patients for whom cisplatin-based treatment is unsuitable according to the inclusion criteria of the studies. Unsuitability for cisplatin was determined based on the presence of at least one of the following criteria according to Galsky 2011 [9]: ECOG PS ≥ 2 or Karnofsky performance score of 60% to 70%, reduced renal function, hearing loss (CTCAE grade ≥ 2), peripheral neuropathy (CTCAE grade ≥ 2) or NYHA class III heart

failure. Publications defining patients as unsuitable for cisplatin-based chemotherapy could also be included.

The study characteristics and the interventions used are summarized in Appendix A, Table 10 and Table 11, of the full dossier assessment.

In addition to the main analysis, the company presented a sensitivity analysis of patients who had received first-line treatment with carboplatin + gemcitabine for locally advanced or metastatic urothelial carcinoma, but for whom it was unclear whether cisplatin-containing therapy was suitable based on the inclusion criteria. Six additional single-arm studies and one arm of an RCT were included in the sensitivity analysis. Since these studies possibly also included patients for whom therapy with cisplatin was suitable, these studies were rated as irrelevant and are not considered further.

Based on its main analysis, the company derived a hint of a non-quantifiable added benefit for adult patients with advanced or metastatic urothelial carcinoma for whom cisplatin-containing first-line treatment is unsuitable. The company based this result mainly on the results on overall survival and on individual AE outcomes.

The company's assessment was not shared.

Data situation

Differences between atezolizumab and carboplatin + gemcitabine in overall survival not large enough

The outcome "overall survival" was only reported in 4 of the 5 comparator studies for the main analysis. The company conducted 4 individual comparisons versus the IMvigor210 study, deriving major added benefit for 2 comparisons and no added benefit for the other 2 comparisons. The company conducted no joint consideration or summarizing balancing of the effects on overall survival.

The certainty of results was low due to the comparison of individual arms of different studies conducted by the company. The effect sizes (hazard ratio [HR] with confidence interval [CI]) shown by the company on overall survival were not large enough (versus [HR [CI], p-value] Bamias 2007: 0.62 [0.36; 1.04]; 0.072, Carles 2000: 0.63 [0.31; 1.27], 0.196, Linardou: 2004: 0.45 [0.30; 0.67]; < 0.001 and De Santis 2012: 0.58 [0.43; 0.80]; < 0.001) to exclude that they were caused only by confounding factors.

A conclusion on the added benefit for the outcome "overall survival" is therefore not possible on the basis of the results presented.

Incomplete data and differences between atezolizumab and carboplatin + gemcitabine in overall rates of adverse events not large enough

Relevant outcomes were partly not reported in the publications on the studies included by the company. Table 5 shows for which outcomes data were available in the publications of the studies included by the company.

Table 5: Overview of the outcomes reported in the studies – further investigations: atezolizumab vs. carboplatin + gemcitabine

Study	Outcomes							
	Overall survival	Morbidity	Health-related quality of life	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs	Immunotherapy-specific AEs	Chemotherapy-specific AEs
Study with atezolizumab								
IMvigor210	●			●	●[a]	●	●[b]	●
Studies with carboplatin + gemcitabine[c]								
Bamias 2007	●	(●[d])	(●[d])			●		●
Bellmunt 2001								●
Carles 2000	●							●
Linardou 2004	●							●
De Santis 2012	●	(●[d])	(●[d])			●		●

a: For the IMvigor210 study, severe CTCAE grade ≥ 3 AEs were also reported in Module 4 of the dossier.
b: Incomplete presentation of immune-related AEs in Module 4 of the dossier.
c: Only the studies of the main analysis are considered.
d: Recorded with the EORTC QLQ-C30. Results were reported only incompletely in the publication.
●: data available; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SAE: serious adverse event; vs.: versus

The company's dossier contained overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3) only for the IMvigor210 study. These outcomes were not reported in the comparator studies (see Table 5). The overall rates of AEs leading to discontinuation of the treatment were reported in only 2 of the 5 comparator studies. In comparison with these studies, there was a statistically significant effect in favour of atezolizumab for this outcome. Based on these data, the company derived a minor added benefit of atezolizumab for the outcome "discontinuation due to AEs". The difference between the treatments was not large enough not to be explicable only by confounding factors, however. Hence the data on the overall rates of side effects were overall unsuitable to draw a conclusion on the added benefit of atezolizumab.

Incomplete data on the comparison of individual outcomes on specific adverse events

The company additionally presented different individual outcomes on specific severe CTCAE grade 3 and 4 AEs (only grade 1 or 2 for alopecia) at the level of the System Organ Class (SOC), Preferred Terms (PTs) and Lowest Level Terms (LLTs) of the Medical Dictionary for Regulatory Activities (MedDRA), which were recorded both in the IMvigor210 study and in at least one of the comparator studies. In its comparison, the company rated the large effect differences in favour of atezolizumab for the specific AEs "granulocytopenia", "leukopenia", "neutropenia" and "thrombocytopenia" (all CTCAE grade 3 and 4) as dramatic and derived major added benefit of atezolizumab versus carboplatin + gemcitabine from this.

This assessment of the lesser harm from atezolizumab was inadequate. For the outcomes mentioned, there was an effect in favour of atezolizumab that cannot be explained by confounding factors alone. However, the choice of AEs in the present comparison was restricted to AEs presented in at least one of the comparator studies that only investigated chemotherapies. The haematologic toxicities identified by the company are characteristic and common class effects of chemotherapeutic agents such as carboplatin [10]. In contrast, immune-related AEs characteristic of immunotherapeutic agents such as atezolizumab were not reported in the comparator studies (see Table 5). In its dossier, the company described the IMvigor210 study data on AEs associated with immunotherapy, but did not put them into a context allowing an estimation of the extent of the observed AEs in the present therapeutic indication. Furthermore, the operationalization of immune-related AEs in the IMvigor210 study was based on a list of prespecified AEs and was therefore unsuitable to record all immune-related AEs of the IMvigor210 study.

The data and the company's consideration on specific side effects were therefore incomplete and allowed no comprehensive comparison of the specific side effects of atezolizumab versus carboplatin + gemcitabine.

Outcomes on morbidity and health-related quality of life not recorded

Neither the IMvigor210 study nor the majority of the comparator studies recorded outcomes on morbidity or health-related quality of life. Hence no comparable data were available for these outcome categories (see Table 5).

Restriction of the appropriate comparator therapy

The company chose carboplatin + gemcitabine as the only relevant comparator therapy because it considered this therapy to concur with the regular treatment specified by a physician on the basis of rational decision criteria and current guideline recommendations.

This approach was not followed. The German S3 guideline explicitly states that there is no standard therapy for patients for whom cisplatin-containing treatment is unsuitable because of the heterogeneity of this patient population [11]. For patients with an ECOG PS of 0 or 1, the guideline recommends treatment with carboplatin + gemcitabine although this treatment is not approved for this therapeutic indication. Patients with an ECOG PS of 2 or higher can be

treated with monochemotherapy, according to the guideline [11]. Particularly patients with an unfavourable risk profile (ECOG PS ≥ 2 and reduced renal function or Bajorin risk group 2) have only little benefit from carboplatin-based combination therapy [8,11,12]. It should be noted that each of the studies included by the company for the main analysis included a relevant proportion of patients with ECOG PS ≥ 2 or Karnofsky performance score ≤ 70% (19–68%). In addition, all studies used reduced renal function as a criterion for unsuitability for cisplatin-containing therapy. It was therefore unclear to what extent carboplatin + gemcitabine concurred with the treatment specified by the physician for all patients considered. Hence as a result of the company's restriction of the comparator therapy to only carboplatin + gemcitabine, the ACT defined by the G-BA – chemotherapy specified by the physician – was not completely represented.

Summary

In summary, the incomplete data situation allowed no adequate comparison between atezolizumab and carboplatin + gemcitabine. In addition, conclusions on the added benefit based on a comparison of individual arms of different studies can only be drawn in the presence of very large effects due to the high uncertainty of results. There were 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 (CTCAE grade ≥ 3) AEs. Due to the incomplete information provided on specific AEs, no comprehensive assessment of these AEs was possible.

As a result of the company's restriction of the comparator therapy to only carboplatin + gemcitabine, the ACT defined by the G-BA – chemotherapy specified by the physician – was not completely represented.

Overall, no suitable data were available for the assessment of atezolizumab in adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing first-line treatment is unsuitable.

2.4 Results on added benefit

No suitable data were available for the assessment of atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma in adult patients for whom cisplatin-containing first-line treatment is unsuitable. Hence there was 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

The result of the assessment of the added benefit of atezolizumab in comparison with the ACT is summarized in Table 6.

Table 6: Atezolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable (first-line treatment)	Chemotherapy specified by the physician	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This assessment deviates from that of the company, which derived a hint of a non-quantifiable added benefit of atezolizumab in comparison with carboplatin + gemcitabine as ACT.

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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017; 389(10064): 67-76.

4. Bamias A, Lainakis G, Kastritis E, Antoniou N, Alivizatos G, Koureas A et al. Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. Oncology 2007; 73(5-6): 290-297.

5. Bellmunt J, De Wit R, Albanell J, Baselga J. A feasibility study of carboplatin with fixed dose of gemcitabine in "unfit" patients with advanced bladder cancer. Eur J Cancer 2001; 37(17): 2212-2215.

6. Carles J, Nogue M, Domenech M, Perez C, Saigi E, Villadiego K et al. Carboplatin-gemcitabine treatment of patients with transitional cell carcinoma of the bladder and impaired renal function. Oncology 2000; 59(1): 24-27.

7. Linardou H, Aravantinos G, Efstathiou E, Kalofonos C, Anagnostopoulos A, Deliveliotis C et al. Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: phase II study of the Hellenic Co-operative Oncology Group. Urology 2004; 64(3): 479-484.

8. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012; 30(2): 191-199.

9. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 2011; 29(17): 2432-2438.

10. Fresenius Kabi. Carboplatin Kabi 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 12.2016 [Accessed: 09.06.2017]. URL: http://www.fachinfo.de.

11. Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Deutsche Krebsgesellschaft, Deutsche Krebshilfe. S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms: Langversion 1.1; AWMF-Registrierungsnummer 032/038OL (Stand: November 2016) [online]. [Accessed: 05.08.2017]. URL: http://leitlinienprogramm-onkologie.de/Harnblasenkarzinom.92.0.html.

12. Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999; 17(10): 3173-3181.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-51-atezolizumab-urothelial-carcinoma-first-line-treatment-benefit-assessment-according-to-35a-social-code-book-v.8024.html.