Nivolumab
(urothelial carcinoma, first-line treatment)

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

EXTRACT

Project: A24-70 Version: 1.0 Status: 19 Sep 2024 DOI: 10.60584/A24-70_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Nivolumab (Urothelkarzinom, Erstlinientherapie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Nivolumab (urothelial carcinoma, first-line treatment) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

27 June 2024

Internal Project No.

A24-70

DOI-URL

https://doi.org/10.60584/A24-70_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

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

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, Germany

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Alfred Marenbach and one other person.

IQWiG thanks the respondents as well as the patient organizations “Bundesverband Niere e. V.” and “Selbsthilfe-Bund Blasenkrebs e. V.” for participating in the written exchange and for their support. The respondents, the “Bundesverband Niere e. V.” and the “Selbsthilfe-Bund Blasenkrebs e. V.” were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Michael Hort
- Christiane Balg
- Kirsten Janke
- Claudia Kapp
- Philip Kranz
- Sabine Ostlender
- Mattea Patt
- Pamela Wronski

Keywords

Nivolumab, Urologic Neoplasms, Carcinoma – Transitional Cell, Benefit Assessment, NCT03036098

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
BSA	body surface area
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 nivolumab (in combination with cisplatin and gemcitabine). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 27 June 2024.

Research question

The aim of the present report is the assessment of the added benefit of nivolumab in combination with cisplatin and gemcitabine (hereinafter referred to as nivolumab + cisplatin + gemcitabine) compared with the appropriate comparative therapy (ACT) for first-line treatment of adult patients with unresectable or metastatic urothelial 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 nivolumab + cisplatin + gemcitabine

Therapeutic indication	**ACT[a]**
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for patients who are progression-free[b])
a. Presented is the ACT specified by the G-BA. b. According to G-BA, it is assumed that patients who are not progression-free following cisplatin-based chemotherapy will not continue to be treated as part of first-line treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. With regard to the ACT, the company also stated that the therapy should be carried out in the dosages and regimens approved for Germany according to the Summary of Product Characteristics (SPC), and real-world clinical care in Germany. With reference to Als 2008, the company described that, deviating from the SPC, chemotherapy with cisplatin and gemcitabine is administered as 21-day cycles in German clinical care practice. Therefore, for its assessment, the company also considered studies in which chemotherapy was administered according to this treatment regimen. This is of no consequence for the present assessment, as no suitable data are available to compare nivolumab + cisplatin + gemcitabine with the ACT.

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

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of nivolumab + cisplatin + gemcitabine in comparison with the ACT. The company, in contrast, identified the RCT CA209-901 and used it in its assessment. The CA209-901 study is not suitable for the benefit assessment, since the study protocol did not provide for maintenance therapy with avelumab for patients in the comparator arm who were progression-free following chemotherapy. Avelumab was also only used in a small proportion of patients in the comparator arm as part of the follow-up therapies administered. Based on the available data, it can therefore be concluded that for a relevant proportion of the included patients, the ACT was not implemented. The CA209-901 study is described below, and the unsuitability is justified.

Evidence presented by the company – CA209-901 study

The CA209-901 study is an ongoing, multicentre, randomized, open-label phase 3 study with a total of 4 treatment arms, which compares nivolumab + cisplatin + gemcitabine with cisplatin + gemcitabine in a substudy. The following will only address this substudy.

The substudy included adult patients with unresectable or metastatic urothelial carcinoma who were eligible for cisplatin-based chemotherapy. Accordingly, patients had to have an Eastern Cooperative Oncology Group performance status of ≤ 1 and adequate renal function (glomerular filtration rate ≥ 60 mL/min). Patients with previous systemic chemotherapy for unresectable or metastatic urothelial carcinoma were excluded. Adjuvant or neoadjuvant therapy was allowed if disease recurrence happened at least 12 months after completion of such therapy.

The substudy for CA209-901 included a total of 608 patients who were randomly allocated in a 1:1 ratio to either nivolumab + cisplatin + gemcitabine (N = 304) or cisplatin + gemcitabine (N = 304).

Treatment with nivolumab + cisplatin + gemcitabine in the intervention arm of the substudy was largely in compliance with the specifications of the SPC. Initially, nivolumab was administered in combination with gemcitabine and cisplatin in 21-day treatment cycles for up to 6 cycles, with nivolumab (360 mg) on day 1, gemcitabine (1000 mg/m^2 body surface area [BSA]) on days 1 and 8, and cisplatin (70 mg/m^2 BSA) on day 1. Following the combination therapy, nivolumab was administered as monotherapy at a dose of 480 mg every 4 weeks.

In the comparator arm of the substudy, the platinum-based chemotherapy was administered in 21-day treatment cycles (for up to 6 cycles) at the same dosage as in the intervention arm. According to the SPC, however, treatment with gemcitabine in combination with cisplatin should take place in 28-day treatment cycles, with gemcitabine (1000 mg/m^2 BSA) on days 1, 8 and additionally on day 15 of each cycle. This deviation is of no consequence for the present

assessment, as the data from the substudy are not suitable for comparing nivolumab + cisplatin + gemcitabine with the ACT.

The primary outcomes of the substudy are overall survival and progression-free survival (PFS). Secondary outcomes are recorded in the categories of morbidity, health-related quality of life, and side effects.

ACT not implemented in the CA209-901 study

The G-BA has defined treatment with cisplatin in combination with gemcitabine as ACT for first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. For patients who are progression-free after chemotherapy, maintenance therapy with avelumab should be carried out in accordance with the G-BA's decision. The substudy comparing nivolumab + cisplatin + gemcitabine with cisplatin + gemcitabine, however, did not provide for maintenance therapy with avelumab in the comparator arm for patients who were progression-free following chemotherapy.

The company stated that maintenance therapy with avelumab for patients without progression was not explicitly provided for in the study protocol and that not all patients without progression received corresponding maintenance therapy. However, it does not provide any information on the proportion of patients in the comparator arm of the substudy affected by this. Based on the available data, however, it can be assumed that maintenance therapy with avelumab would have been indicated for a relevant proportion of patients.

In the substudy, avelumab was only used in a small proportion of patients in the comparator arm as part of the follow-up therapies administered. Information in Module 5 of the dossier shows that only 27 patients (9%) who had completed treatment in the comparator arm received follow-up treatment with avelumab without prior documented progression. For the remaining patients in the comparator arm, it is not clear from the information in the dossier whether treatment with avelumab according to the ACT would have been indicated. To assess this, it would be necessary to know how many patients in the comparator arm received at least 4 cycles of cisplatin + gemcitabine and were subsequently progression-free. Such information was not available in the dossier, however.

However, the available data on PFS show that 119 patients (39%) in the comparator arm of the substudy were still at risk of progression at month 6 and that maintenance therapy with avelumab would therefore have been indicated for these patients. Assuming that all of the aforementioned 27 patients (9%) in the comparator arm who received avelumab as follow-up therapy fell into this patient group and were treated in accordance with avelumab’s SPC, at least another 30% of the patients in the comparator arm should have received avelumab therapy. The proportion of patients for whom the ACT was implemented in the comparator arm of the substudy is therefore not sufficient to use if for the benefit assessment.

It can also be assumed that the proportion of patients for whom the ACT was not implemented is potentially significantly higher than 30%. This is due in particular to the fact that maintenance therapy with avelumab would also potentially have been indicated for patients with progression events between month 3 and month 6 if the progression event had occurred after the end of chemotherapy. On the one hand, treatment with chemotherapy was already completed at week 18 (corresponding to around 4 months) due to the 21-day treatment cycle in the comparator arm of the substudy, so avelumab could have been used at this point in patients without progression. On the other hand, maintenance therapy with avelumab would also have been possible after 4 cycles of chemotherapy (corresponding to around month 3) in accordance with the SPC if treatment in the comparator arm had been discontinued prematurely without progression or if the patient had died. According to the Kaplan-Meier curve for PFS, 223 patients (73%) in the comparator arm of the substudy were still at risk of progression at month 3. Given this context, it can be assumed that the actual proportion of patients in the comparator arm for whom maintenance therapy with avelumab would potentially have been indicated is significantly higher than 30%. The ACT was thus not implemented for a relevant proportion of patients and the substudy is therefore not suitable for the benefit assessment.

Overall, based on the available data, it is clear that the ACT was not implemented for a relevant proportion of patients in the comparator arm of the substudy. The results of the substudy presented by the company are therefore not suitable for the present benefit assessment and the study is not used for the assessment.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of nivolumab + cisplatin + gemcitabine in comparison with the ACT; an added benefit is therefore not proven.

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

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

[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 3: Nivolumab + cisplatin + gemcitabine – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for patients who are progression-free[b])	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to G-BA, it is assumed that patients who are not progression-free following cisplatin-based chemotherapy will not continue to be treated as part of first-line treatment.

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is the assessment of the added benefit of nivolumab in combination with cisplatin and gemcitabine (hereinafter referred to as nivolumab + cisplatin + gemcitabine) compared with the appropriate comparative therapy (ACT) for first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

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 nivolumab + cisplatin + gemcitabine

Therapeutic indication	**ACT**[a]
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for patients who are progression-free[b])
a. Presented is the ACT specified by the G-BA. b. According to G-BA, it is assumed that patients who are not progression-free following cisplatin-based chemotherapy will not continue to be treated as part of first-line treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. With regard to the ACT, the company also stated that the therapy should be carried out in the dosages and regimens approved for Germany according to the SPC, and real-world clinical care in Germany. With reference to AIs 2008 [3], the company described that, deviating from the SPC, chemotherapy with cisplatin and gemcitabine is administered as 21-day cycles in German clinical care practice. Therefore, for its assessment, the company also considered studies in which chemotherapy was administered according to this treatment regimen. This is of no consequence for the present assessment, as no suitable data are available to compare nivolumab + cisplatin + gemcitabine with the ACT (for reasons, see Chapter I 3).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive 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 nivolumab (status: 14 May 2024)
- bibliographical literature search on nivolumab (last search on 14 May 2024)
- search in trial registries / trial results databases for studies on nivolumab (last search on 14 May 2024)
- search on the G-BA website for nivolumab (last search on 14 May 2024)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 8 July 2024); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of nivolumab + cisplatin + gemcitabine in comparison with the ACT for the present research question.

The company, in contrast, identified the RCT CA209-901 [4-8] and used it for its assessment. The CA209-901 study is not suitable for the benefit assessment, since the study protocol did not provide for maintenance therapy with avelumab for patients in the comparator arm who were progression-free following chemotherapy. Avelumab was also only used in a small proportion of patients in the comparator arm as part of the follow-up therapies administered. Based on the available data, it can therefore be concluded that for a relevant proportion of the included patients, the ACT was not implemented. The CA209-901 study is described below, and the unsuitability is justified.

Evidence provided by the company

Design of the CA209-901 study

The CA209-901 study is an ongoing, multicentre, randomized, open-label phase 3 study comprising a primary study and a substudy, each with 2 treatment arms. In the primary study (study arm A vs. B), nivolumab in combination with ipilimumab, followed by monotherapy with nivolumab, is compared with platinum-based chemotherapy (cisplatin or carboplatin, in each case in combination with gemcitabine). In the substudy (study arm C vs. D), nivolumab in combination with cisplatin-based chemotherapy, followed by monotherapy with nivolumab, is compared with cisplatin-based chemotherapy, with cisplatin being used in

combination with gemcitabine as chemotherapy in arms C and D. The following discussion will focus exclusively on the sub-study comparing nivolumab + cisplatin + gemcitabine with cisplatin + gemcitabine.

The substudy included adult patients with unresectable or metastatic urothelial carcinoma who were eligible for cisplatin-based chemotherapy. Accordingly, patients had to have an Eastern Cooperative Oncology Group performance status of ≤ 1 and adequate renal function (glomerular filtration rate ≥ 60 mL/min). Patients with previous systemic chemotherapy for unresectable or metastatic urothelial carcinoma were excluded. Adjuvant or neoadjuvant therapy was allowed if disease recurrence happened at least 12 months after completion of such therapy.

The substudy included a total of 608 patients who were randomly allocated in a 1:1 ratio to either nivolumab + cisplatin + gemcitabine (N = 304) or cisplatin + gemcitabine (N = 304). Randomization was stratified according to programmed cell death ligand 1 (PD-L1) tumour cell status (< 1% vs. ≥ 1%) and the presence of liver metastases (yes vs. no).

Treatment with nivolumab + cisplatin + gemcitabine in the intervention arm of the substudy was largely in compliance with the specifications of the SPC [9]. Initially, nivolumab was administered in combination with gemcitabine and cisplatin in 21-day treatment cycles for up to 6 cycles, with nivolumab (360 mg) on day 1, gemcitabine (1000 mg/m^2 body surface area [BSA]) on days 1 and 8, and cisplatin (70 mg/m^2 BSA) on day 1. Following the combination therapy, nivolumab was administered as monotherapy at a dose of 480 mg every 4 weeks. Treatment with the intervention was carried out over a total of up to 24 months.

In the comparator arm of the substudy, the platinum-based chemotherapy was administered in 21-day treatment cycles at the same dosage as in the intervention arm. According to the SPC [10], however, treatment with gemcitabine in combination with cisplatin should take place in 28-day treatment cycles, with gemcitabine (1000 mg/m^2 BSA) on days 1, 8 and additionally on day 15 of each cycle. This deviation is of no consequence for the present assessment, as the data from the substudy are not suitable for comparing nivolumab + cisplatin + gemcitabine with the ACT. In the comparator arm of the substudy, treatment was administered for up to a maximum of 6 cycles, until disease progression, until the occurrence of unacceptable toxicity, or until withdrawal of consent, whichever occurred earlier.

The primary outcomes of the substudy are overall survival and progression-free survival (PFS). Secondary outcomes are recorded in the categories of morbidity, health-related quality of life, and side effects.

Further details on the CA209-901 study, the interventions used in the substudy, and the characterisation of the patients included in the substudy can be found in I Appendix B of the full dossier assessment.

ACT not implemented in the CA209-901 study

The G-BA has defined treatment with cisplatin in combination with gemcitabine as ACT for first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. For patients who are progression-free after chemotherapy, maintenance therapy with avelumab should be carried out in accordance with the G-BA's decision. The substudy comparing nivolumab + cisplatin + gemcitabine with cisplatin + gemcitabine, however, did not provide for maintenance therapy with avelumab in the comparator arm for patients who were progression-free following chemotherapy.

In Module 4 Y of the dossier, the company argued that the ACT was nevertheless implemented for a relevant proportion of patients. It justified this by stating that for patients who suffered progression or died during or shortly after chemotherapy, the ACT was fully implemented in the study. In addition, according to the study protocol, no maintenance therapy with avelumab was planned in the comparator arm of the study, as cisplatin-based chemotherapy was the standard of care in first-line therapy at the time the study began (January 2018). However, the change in the treatment landscape with the establishment of avelumab as part of first-line therapy for patients without progression was taken into account by the investigators, resulting in 32 patients in the comparator arm (10.5%) receiving subsequent treatment with avelumab during the course of the study. From the company's point of view, the study fulfils the requirements of the G-BA with regard to the appropriate comparator therapy in the best possible way, given the study period. In summary, the company concluded that the validity of the study with regard to an added benefit in the present therapeutic indication is subject to limitations and assumed a moderate certainty of results. From the company's point of view, however, despite the limitations, conclusions on the added benefit of nivolumab + cisplatin + gemcitabine can still be derived from the study with the certainty of conclusions of a hint.

The company’s reasoning is not appropriate. The company stated that maintenance therapy with avelumab for patients without progression was not explicitly provided for in the study protocol and that not all patients without progression received corresponding maintenance therapy. However, it does not provide any information on the proportion of patients in the comparator arm of the substudy affected by this. Based on the available data, however, it can be assumed that maintenance therapy with avelumab would have been indicated for a relevant proportion of patients.

In the substudy, avelumab was only used in a small proportion of patients in the comparator arm as part of the follow-up therapies administered. Information in Module 5 of the dossier shows that only 27 patients (9%) who had completed treatment in the comparator arm received follow-up treatment with avelumab without prior documented progression. No information is provided in the dossier as to when treatment with avelumab was administered to these patients, i.e. how many cycles of chemotherapy had been administered beforehand and when avelumab therapy was started after the end of chemotherapy. Accordingly, it remains unclear whether treatment with avelumab in these patients was carried out in accordance with the avelumab's SPC [11].

For the remaining patients in the comparator arm, it is not clear from the information in the dossier whether treatment with avelumab according to the ACT would have been indicated. To assess this, it would be necessary to know how many patients in the comparator arm received at least 4 cycles of cisplatin + gemcitabine and were subsequently progression-free. Such information was not available in the dossier, however. However, the Kaplan-Meier curve for PFS (see Figure 1 in Appendix B.2) shows that 119 patients (39%) in the comparator arm of the substudy were still at risk of progression at month 6 and that maintenance therapy with avelumab would therefore have been indicated for these patients. Assuming that all of the aforementioned 27 patients (9%) in the comparator arm who received avelumab as follow-up therapy fell into this patient group and were treated in accordance with avelumab's SPC, at least another 30% of the patients in the comparator arm should have received avelumab therapy. The proportion of patients for whom the ACT was implemented in the comparator arm of the substudy is therefore not sufficient to use if for the benefit assessment.

It can also be assumed that the proportion of patients for whom the ACT was not implemented is potentially significantly higher than 30%. This is due in particular to the fact that maintenance therapy with avelumab would also potentially have been indicated for patients with progression events between month 3 and month 6 (see Figure 1) if the progression event had occurred after the end of chemotherapy. On the one hand, treatment with chemotherapy was already completed at week 18 (corresponding to around 4 months) due to the 21-day treatment cycle in the comparator arm of the substudy, so avelumab could have been used at this point in patients without progression. On the other hand, maintenance therapy with avelumab would also have been possible after 4 cycles of chemotherapy (corresponding to around month 3) in accordance with the SPC if treatment in the comparator arm had been discontinued prematurely without progression or if the patient had died. According to the Kaplan-Meier curve for PFS, 223 patients (73%) in the comparator arm of the substudy were still at risk of progression at month 3. Given this context, it can be assumed that the actual proportion of patients in the comparator arm for whom maintenance therapy with avelumab would potentially have been indicated is significantly higher than 30%. The ACT was thus not

implemented for a relevant proportion of patients and the substudy is therefore not suitable for the benefit assessment.

In addition, there is further uncertainty regarding the implementation of the ACT, which would also have to be taken into account in the previously described estimate of the proportion of patients treated according to the G-BA's ACT. For example, it was possible to switch treatment from cisplatin to carboplatin within the study, which the G-BA's ACT does not provide for. According to the information in Module 5 of the dossier, treatment was switched from cisplatin to carboplatin in 43 patients (14%) in the comparator arm of the substudy.

Conclusion

In summary, based on the available data, it is clear that the ACT was not implemented for a relevant proportion of patients in the comparator arm of the substudy. The study is therefore unsuitable for the present benefit assessment.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of nivolumab + cisplatin + gemcitabine in comparison with the ACT for first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. This results in no hint of an added benefit of nivolumab + cisplatin + gemcitabine in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of nivolumab + cisplatin + gemcitabine in comparison with the ACT.

Table 5: Nivolumab + cisplatin + gemcitabine – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for patients who are progression-free[b])	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to G-BA, it is assumed that patients who are not progression-free following cisplatin-based chemotherapy will not continue to be treated as part of first-line treatment.

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

The assessment described above differs from that of the company, which derived a hint of a non-quantifiable added benefit of nivolumab + cisplatin + gemcitabine compared with the ACT based on the results of the CA209-901 study for patients with unresectable or metastatic urothelial carcinoma.

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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Als AB, Sengelov L, Von Der Maase H. Gemcitabine and cisplatin in locally advanced and metastatic bladder cancer; 3- or 4-week schedule? Acta Oncol 2008; 47(1): 110-119. https://doi.org/10.1080/02841860701499382.

4. van der Heijden MS, Sonpavde G, Powles T et al. Nivolumab plus Gemcitabine–Cisplatin in Advanced Urothelial Carcinoma. N Engl J Med 2023; 389(19): 1778-1789. https://doi.org/10.1056/NEJMoa2309863.

5. Bristol-Myers Squibb. Study of Nivolumab in Combination with Ipilimumab or Standard of Care Chemotherapy Compared to the Standard of Care Chemotherapy Alone in Treatment of Participants with Untreated Inoperable or Metastatic Urothelial Cancer (CheckMate901) [online]. 2024 [Accessed: 18.07.2024]. URL: https://clinicaltrials.gov/study/NCT03036098.

6. Bristol-Myers Squibb. A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab, or with Standard of Care Chemotherapy, versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer [online]. [Accessed: 18.07.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-003881-14.

7. Bristol-Myers Squibb. A Phase 3, Open-Label, Randomized Study Of Nivolumab Combined With Ipilimumab, Or With Standard Of Care Chemotherapy, Versus Standard Of Care Chemotherapy In Participants With Previously Untreated Unresectable Or Metastatic Urothelial Cancer; Study CA209901; Interim Clinical Study Report; Final Analysis for CA209901 Substudy [unpublished]. 2023.

8. Bristol-Myers Squibb. A Phase 3, Open-Label, Randomized Study Of Nivolumab Combined With Ipilimumab, Or With Standard Of Care Chemotherapy, Versus Standard Of Care Chemotherapy In Participants With Previously Untreated Unresectable Or Metastatic Urothelial Cancer; Study CA209901; Erratum to Interim Clinical Study Report [unpublished]. 2024.

9. Bristol-Myers Squibb. OPDIVO 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2024 [Accessed: 28.06.2024]. URL: https://www.fachinfo.de/.

10. TEVA. Gemcitabin-GRY 1000 mg Pulver zur Herstellung einer Infusionslösung [online]. 2023 [Accessed: 28.06.2024]. URL: https://www.fachinfo.de/.

11. Merck. Bavencio 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2024 [Accessed: 28.06.2024]. URL: https://www.fachinfo.de/.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-70.html.