IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-29

Nivolumab (urothelial carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Nivolumab (Urothelkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 September 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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[3] 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
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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 (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. 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 3 July 2017.

Research question

The aim of the present report was to assess the added benefit of nivolumab compared with the appropriate comparator therapy (ACT) in adult patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy.

Table 2 shows the research question of the benefit assessment of nivolumab.

Table 2: Research question of the benefit assessment of nivolumab

Subindication	**ACT**[a, b]
Monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy	For patients with early recurrence (≤ 6 months): ▪ vinflunine For patients with late recurrence (> 6 – 12 months): ▪ **vinflunine** or ▪ repeated cisplatin-based chemotherapy[c]
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is assumed for the present therapeutic indication that the treatment options mentioned above equally apply to patients with progression after platinum-based adjuvant/neoadjuvant chemotherapy. c: For patients for whom this is an option, depending on course of disease, general condition and tolerability of the first-line treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. It chose vinflunine from the treatment options presented for patients with late recurrence.

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 5 studies and chose 1 arm from each of them for a comparison of individual arms from different studies for the benefit assessment.

For nivolumab, the company used 1 arm of study CA209-032 (hereinafter referred to as "CheckMate 032") and the single-arm study CA209-275 (hereinafter referred to as "CheckMate 275"). For the ACT vinflunine, the company included 1 arm of each of the studies Bellmunt 2009 and Bellmunt 2017 as well as the single-arm study Vaughn 2009. The patients in the 5 studies included by the company were adults with locally advanced unresectable or metastatic urothelial carcinoma with progression during or after platinum-containing chemotherapy.

The data presented by the company were unsuitable to draw conclusions on the added benefit of nivolumab in comparison with the ACT. This is justified below:

Limitation of the presentation of specific adverse events (AEs) to chemotherapy-induced side effects

The specific severe AEs presented by the company, which it used for the derivation of its added benefit, were an inadequate choice. In this choice, the company limited the analysis of specific AEs to the vinflunine-specific range of side effects with chemotherapy-induced events. The company did not include nivolumab-specific side effects – e.g. the immune-related side effects typical of this monoclonal antibody – in the assessment. This limitation was inadequate.

The company's inadequate choice of specific AEs did not allow an assessment of the added benefit of nivolumab in comparison with vinflunine.

No large differences between nivolumab and vinflunine in the overall rates of AEs

The added benefit of nivolumab in comparison with vinflunine cannot be assessed on the basis of the specific AEs chosen by the company. The data presented by the company on overall rates of severe AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade 3–4, serious AEs (SAEs) and discontinuation due to AEs, in contrast, provide a more complete picture of AEs on both sides of the comparison. In contrast to the data on specific AEs, no large differences between the nivolumab studies and the vinflunine studies were shown. However, an added benefit from comparisons of individual arms from different studies can only be derived in the presence of very large effects.

Large differences between the nivolumab studies and the vinflunine studies were also not shown for the results presented by the company for the outcome "overall survival".

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

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

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

Table 3: Nivolumab – probability and extent of added benefit

Subindication	**ACT[a, b]**	**Probability and extent of added benefit**
Monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy	For patients with early recurrence (≤ 6 months): ▪ vinflunine For patients with late recurrence (> 6 – 12 months): ▪ **vinflunine** or ▪ repeated cisplatin-based chemotherapy[c]	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is assumed for the present therapeutic indication that the treatment options mentioned above equally apply to patients with progression after platinum-based adjuvant/neoadjuvant chemotherapy. c: For patients for whom this is an option, depending on course of disease, general condition and tolerability of the first-line treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report was to assess the added benefit of nivolumab compared with the ACT in adult patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy.

Table 4 shows the research question of the benefit assessment of nivolumab.

Table 4: Research question of the benefit assessment of nivolumab

Subindication	**ACT**[a, b]
Monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy	For patients with early recurrence (≤ 6 months): ▪ vinflunine For patients with late recurrence (> 6 – 12 months): ▪ **vinflunine** or ▪ repeated cisplatin-based chemotherapy[c]
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is assumed for the present therapeutic indication that the treatment options mentioned above equally apply to patients with progression after platinum-based adjuvant/neoadjuvant chemotherapy. c: For patients for whom this is an option, depending on course of disease, general condition and tolerability of the first-line treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. It chose vinflunine from the treatment options presented for patients with late recurrence.

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 nivolumab (status: 5 May 2017)
- bibliographical literature search on nivolumab (last search on 3 May 2017)
- search in trial registries for studies on nivolumab (last search on 4 May 2017)
- bibliographical literature search on the ACT (last search on 5 May 2017)
- search in trial registries for studies on the ACT (last search on 4 May 2017)

To check the completeness of the study pool:

- bibliographical literature search on nivolumab (last search on 13 July 2017)
- search in trial registries for studies on nivolumab (last search on 11 July 2017)
- bibliographical literature search on the ACT (last search on 13 July 2017)
- search in trial registries for studies on the ACT (last search on 14 July 2017)

The check identified no additional relevant study.

Study pool of the company

The company did not identify any randomized controlled trial (RCT) of direct comparison of nivolumab versus the ACT from the steps of information retrieval mentioned. Since the company did not find any comparative studies for indirect comparisons either, it conducted a search for further investigations. In this search, the company identified 5 studies, which it used for a comparison of individual arms from different studies for the benefit assessment.

Table 5 shows the studies included by the company as further investigations.

Table 5: Study pool of the company – further investigations: nivolumab vs. vinflunine

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with nivolumab			
CA209-032 (CheckMate 032[b])	Yes	Yes	No
CA209-275 (CheckMate 275[b])	Yes	Yes	No
Studies with vinflunine			
Bellmunt 2009	No	No	Yes
Bellmunt 2017	No	No	Yes
Vaughn 2009	No	Yes[c]	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this designation.
c: The phase 2 study was sponsored by the company; then vinflunine was sold.
RCT: randomized controlled trial; vs.: versus

For nivolumab, the company identified 1 arm of study CA209-032 (hereinafter referred to as "CheckMate 032") [3] and the single-arm study CA209-275 (hereinafter referred to as "CheckMate 275") [4]. For the ACT vinflunine, the company included 1 arm of each of the studies Bellmunt 2009 [5] and Bellmunt 2017 [6] as well as the single-arm study Vaughn 2009 [7,8].

The patients in the 5 studies included by the company were adults with locally advanced unresectable or metastatic urothelial carcinoma with progression during or after platinum-containing chemotherapy. Most patients were in good general condition (corresponding to an Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1). The patients' general condition according to ECOG PS was not recorded in the Vaughn 2009 study. In the Bellmunt 2009 study, over 70% of the patients included had an ECOG PS of 1, which is why the company presented this study only as sensitivity analysis in its comparison of individual arms from different studies. The company justified this with the explanation that, due to the distribution of the ECOG PS and the relevance of the ECOG PS as prognostic factor, the patients in this study tended to have a poorer prognosis than the patients in the nivolumab studies and that, as a result, the estimations in the historical comparison had a tendency to be biased in favour of nivolumab. Except for the patients in the Bellmunt 2009 study, for which the time points of progression after prior platinum-based chemotherapy were not reported, most patients in both nivolumab studies and in the vinflunine studies were patients with early recurrence (0 to ≤ 6 months).

The 5 studies included by the company in the comparison of individual arms from different studies are described in Table 11, Table 12 and Table 13 in Appendix A of the full dossier assessment.

Table 6 shows an overview for which outcomes the company provided data in Module 4 H of the dossier.

Table 6: Overview of the data available in Module 4 H – further investigations: nivolumab vs. vinflunine

Study	Outcomes							
	Overall survival	**Morbidity (EORTC QLQ-C30 and EQ-5D VAS)**	**Health-related quality of life (EORTC QLQ-C30)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade 3–4)[a]**	**Nivolumab-specific AEs**	**Vinflunine-specific AEs**
Nivolumab studies	Yes	Yes	Yes	Yes	Yes	Yes	(No)[b]	Yes
Vinflunine studies	Yes	No[c]	No[c]	Yes	Yes	Yes	No[c]	Yes

a: Severe AEs of CTCAE grade ≥ 3 were also reported for the nivolumab studies.
b: In Module 4 H of the dossier, the company presented only severe AEs (PT and SOC) of CTCAE grade 3–4 with a frequency of ≥ 5%.
c: Outcome not reported in the publications on the vinflunine studies.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

For the nivolumab studies, the company presented data on overall survival, morbidity, health-related quality of life and AEs. For nivolumab-specific AEs, it presented only severe AEs of CTCAE grade 3–4 with a frequency of ≥ 5%. For the vinflunine studies, in contrast, data were available on overall survival and AEs, but not on morbidity and health-related quality of life.

Based on a comparison of individual arms from different studies, the company overall derived a hint of a major added benefit of nivolumab in comparison with vinflunine for patients with early and late recurrence. The company based its assessment on large differences between nivolumab and vinflunine for specific severe AEs (CTCAE grade 3–4). It rated the effects of leukopenia and neutropenia as dramatic. In addition, the company derived an added benefit at outcome level from statistically significant differences for the overall rate of severe AEs (CTCAE grade 3–4) and for individual severe AEs of CTCAE grade 3–4 (anaemia, febrile

neutropenia, thrombocytopenia, treatment discontinuation due to severe neutropenia/leukopenia).

The company's assessment on the added benefit was not followed because the data presented by the company were unsuitable to derive an added benefit of nivolumab in comparison with the ACT. This is justified below.

Limitation of the presentation of specific AEs to chemotherapy-induced side effects

For AEs, the company presented results on the overall rates of AEs (AEs of CTCAE grade 3-4, SAEs, discontinuation due to AEs) in its dossier. In addition, it described results on specific AEs of CTCAE grade 3–4 (anaemia, febrile neutropenia, leukopenia, neutropenia, thrombocytopenia, treatment discontinuation due to febrile neutropenia, treatment discontinuation due to severe neutropenia/leukopenia). The company justified the choice of the AE categories presented and the specific AEs of CTCAE grade 3–4 with the availability of the data for nivolumab and vinflunine.

The choice of specific AEs was not accepted. The specific severe AEs presented by the company, which it used for the derivation of its added benefit, were an inadequate choice. In this choice, the company limited the analysis of specific AEs to the vinflunine-specific range of side effects with chemotherapy-induced events. The company did not include nivolumab-specific side effects [9] – e.g. the immune-related side effects typical of this monoclonal antibody – in the assessment. This limitation of specific AEs to chemotherapy-induced events and the derivation of an added benefit based on events with such limitation was inadequate.

Nivolumab-specific immune-related AEs are presented as additional information in Appendix B (Table 14 and Table 15) of the full dossier assessment. Except for endocrine immune-related AEs, only results for patients treated with immunomodulating drugs were available. To provide an overall picture of the AEs that occurred in both nivolumab studies, severe AEs (CTCAE grade 3–4 and 5) are additionally presented (see Table 16 and Table 17 in Appendix B of the full dossier assessment).

The inadequate choice of specific AEs presented by the company in Module 4 H did not allow an assessment of the added benefit of nivolumab in comparison with vinflunine.

No large differences between nivolumab and vinflunine in the overall rates of AEs

The added benefit of nivolumab in comparison with vinflunine cannot be assessed on the basis of the specific AEs chosen by the company. The data presented by the company on overall rates of severe AEs of CTCAE grade 3–4, SAEs, and discontinuation due to AEs (see Table 18 in Appendix B) provide a more complete picture of AEs on both sides of the comparison. In contrast to the data on specific AEs, no large differences between the nivolumab studies and the vinflunine studies were shown. However, an added benefit from comparisons of individual arms from different studies can only be derived in the presence of very large effects.

Large differences between the nivolumab studies and the vinflunine studies were also not shown for the results presented by the company for the outcome “overall survival”.

2.4 Results on added benefit

No suitable data were available for the assessment of nivolumab in adult patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy. Hence there was no hint of an added benefit of nivolumab 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 nivolumab in comparison with the ACT is summarized in Table 7.

Table 7: Nivolumab – probability and extent of added benefit

Subindication	**ACT**[a, b]	**Probability and extent of added benefit**
Monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy	For patients with early recurrence (≤ 6 months): ▪ vinflunine For patients with late recurrence (> 6 – 12 months): ▪ **vinflunine** or ▪ repeated cisplatin-based chemotherapy[c]	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA’s specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is assumed for the present therapeutic indication that the treatment options mentioned above equally apply to patients with progression after platinum-based adjuvant/neoadjuvant chemotherapy. c: For patients for whom this is an option, depending on course of disease, general condition and tolerability of the first-line treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a hint of a major added benefit of nivolumab in comparison with vinflunine as ACT.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no suitable 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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