IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pembrolizumab (urothelial carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pembrolizumab (Urothelkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 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-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life Questionnaire 5
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPCs	Summaries of Product Characteristics
VAS	visual analogue scale

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 pembrolizumab. 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 11 September 2017.

Research question

The aim of this report was to assess the added benefit of pembrolizumab compared with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic urothelial carcinoma.

The G-BA distinguished between different patient groups in its specification of the ACT. This resulted in 2 research questions for the assessment. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of pembrolizumab

Research question	Subindication	ACT[a]
1	Patients for whom cisplatin-based therapy is not an option (first line)	Chemotherapy specified by the physician
2	Patients after pretreatment with platinum-based chemotherapy	In case of early recurrence (≤ 6 months): ▪ vinflunine In case of late recurrence (> 6 to 12 months): ▪ vinflunine or ▪ repeated platinum-based chemotherapy (for patients for whom this is an option, depending on course of disease, general condition and tolerability of the first-line treatment)
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

For research question 1, the company specified carboplatin + gemcitabine to be the only relevant comparator therapy. Besides vinflunine, the company also specified paclitaxel and docetaxel as ACT for research question 2. This approach was not followed, assessment of the added benefit was conducted versus 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

Research question 1: Patients for whom cisplatin-based chemotherapy is unsuitable (first line)

Study pool of the company

The company presented a comparison of individual study arms for the investigation of this research question. The company compared results on pembrolizumab from the single-arm study KEYNOTE 052 with results on the comparator therapy carboplatin + gemcitabine from a total of 6 studies. These were 4 single-arm studies (Bellmunt 2001, Carles 2000, Linardou 2004, Sella 2012) as well as one study arm from a randomized controlled trial (RCT; De Santis 2012) and one from a retrospective study (Kim 2015).

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

The KEYNOTE 052 study was a single-arm study with adult patients with locally advanced or metastatic urothelial carcinoma who had not received prior therapy for this stage of the disease and for whom cisplatin-based therapy was unsuitable. Non-eligibility for cisplatin-based treatment was defined by a poor general condition (Eastern Cooperative Oncology Group Performance Status [ECOG-PS] 2), kidney dysfunctions, moderate to severe hearing loss, moderate to severe neuropathies or cardiac failure. The patients received pembrolizumab in accordance with the approval.

All 6 studies on carboplatin + gemcitabine considered adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-based therapy was unsuitable.

The company conducted a purely descriptive comparison of study results on pembrolizumab in comparison with carboplatin + gemcitabine, which was additionally based on an incomplete data situation.

Thus, the studies on carboplatin + gemcitabine identified by the company provided only few usable data on patient-relevant outcomes. Results on overall survival were only found in 4 of the 6 studies on carboplatin + gemcitabine, none of these 6 studies included information on morbidity or health-related quality of life. The studies reported results on adverse events (AEs) for particular selected outcomes, which, moreover, were not identical in all studies. Overall rates on serious AEs (SAEs), severe AEs or discontinuation due to AEs are missing in all 6 publications.

The certainty of results was low due to the comparison of individual arms of different studies conducted by the company. The median overall survival in the KEYNOTE 052 study was 11.0 months (95% CI: [10.0; 13.6]), in the comparative studies on carboplatin + gemcitabine it ranged between 7.2 and 10 months. It cannot be excluded that an effect of this size was caused by bias alone (for one or several reasons).

Irrespective of this, the company chose carboplatin + gemcitabine as only comparator therapy. The G-BA specified a therapy chosen by the physician as ACT.

In summary, usable data were not available for the assessment of pembrolizumab in adult patients with locally or metastatic urothelial carcinoma for whom cisplatin-based first-line therapy is not an option.

Research question 2: patients after pretreatment with platinum-based chemotherapy

Study pool and study characteristics

The KEYNOTE 045 study was also included in the assessment of research question 2. This was a RCT on the comparison of pembrolizumab with a chemotherapy. The study population comprised adult patients with locally advanced or metastatic urothelial carcinoma after platinum-based chemotherapy.

Treatment in both study arms was largely conducted in accordance with the respective Summaries of Product Characteristics (SPCs). Among other things, treatment in both study arms should be continued until progression, occurrence of unacceptable side effects of the maximum treatment duration, or until participation was discontinued by investigators or patients. In the pembrolizumab arm, treatment could also be discontinued in case of complete response, if the previous treatment period had been at least 24 weeks. Treatment of clinically stable patients with pembrolizumab could be continued at the investigator's discretion after occurrence of a first progression, until progression was confirmed by a second examination with the help of imaging techniques after at least 4 weeks. Primary outcomes of the study were overall survival and progression-free survival. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and AEs.

In addition to vinflunine, patients of the chemotherapy comparator arm of the KEYNOTE 045 study could also be administered paclitaxel or docetaxel as therapy option for the comparator arm of the study. However, the subpopulation relevant for the benefit assessment comprised only those patients from the pembrolizumab or the comparator group who, on allocation to the comparator group, would have or had received vinflunine. Prior to randomization, a physician chose the treatment to be given to each patient if they were allocated to the comparator group. Hence, analyses for the relevant subpopulation of the study are basically possible without the randomization having to be rendered ineffective.

In its dossier, the company presented the data for the total population of the study, but additionally conducted subgroup analyses for the characteristic "type of chemotherapy" (vinflunine, paclitaxel or docetaxel). Therefore, results on most patient-relevant outcomes are available for the relevant subpopulation.

Risk of bias at study level and outcome level

The risk of bias at study level was rated as low for the KEYNOTE 045 study.

The risk of bias for overall survival at outcome level was rated as low. The risk of bias was high for all other outcomes included.

In the study, the outcomes on "symptoms" and "health-related quality of life" were recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). The visual analogue scale (VAS) of the European Quality of Life Questionnaire 5 (EQ-5D) can be used for the outcome category "general health status". The high risk of bias for these patient-reported outcomes was caused by the open-label study design alone. Moreover, numerous treatment discontinuations occurred, which resulted in potentially informative censorings in the survival time analyses for these outcomes. In addition, discontinuation frequencies differed in several reasons for treatment discontinuation. Nor was there any information on the number of patients for whom at least one further value was available after the start of the study. Patients for whom only one value had been available at the start of the study were presumably censored immediately after the start of the study and thus provided no information for the analysis.

The high risk of bias for all outcomes on side effects also resulted from potentially informative censorings, for the outcome "discontinuation due to AEs" it could also be ascribed to the open-label study design.

In summary, at most an indication, e.g. of an added benefit, can be derived for the outcome "overall survival", and at most a hint can be derived for the other outcomes.

Results

Overall survival

A statistically significant difference in favour of pembrolizumab was shown for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab in comparison with vinflunine for this outcome.

Morbidity - symptoms, recorded using the symptom scales of the EORTC QLQ-C30

Statistically significant differences between the treatment groups in favour of pembrolizumab were shown for the outcomes "nausea and vomiting", "dyspnoea", "loss of appetite" and "constipation". The effect shown for the outcome "dyspnoea" was no more than marginal, which resulted in no hint of an added benefit. For the outcomes "nausea and vomiting", "loss of appetite" and "constipation", there was a hint of an added benefit of pembrolizumab in comparison with vinflunine.

There were no statistically significant differences between the treatment groups for the outcomes "fatigue", "pain", "insomnia" and "diarrhoea". Hence, there was no hint of an added benefit of pembrolizumab in comparison with vinflunine; an added benefit for these outcomes is therefore not proven.

Morbidity – health status, recorded using the EQ-5D VAS

There was no statistically significant difference between the treatment arms for the outcome "health status", irrespective of whether deterioration is based on a threshold value of 10 or 7 points. This resulted in no hint of an added benefit of pembrolizumab in comparison with vinflunine; an added benefit is therefore not proven for this outcome.

Health-related quality of life - EORTC QLQ-C30, functional scales

A statistically significant difference between the treatment groups was not shown for any of the functional scales of the EORTC QLQ-C30. This resulted in no hint of an added benefit of pembrolizumab in comparison with vinflunine; an added benefit is therefore not proven for the outcome "health-related quality of life".

Side effects - SAEs

A statistically significant difference in favour of pembrolizumab was shown for the outcome "SAEs". This resulted in a hint of lesser harm from pembrolizumab in comparison with vinflunine for this outcome.

Side effects - severe AEs (Common Terminology Criteria for AEs [CTCAE] grade ≥ 3)

A statistically significant difference in favour of pembrolizumab was shown for the outcome "severe AEs". This resulted in a hint of lesser harm from pembrolizumab in comparison with vinflunine for this outcome.

Side effects – discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab in comparison with vinflunine; greater or lesser harm is therefore not proven for this outcome.

Side effects - immune-related AEs and further specific AEs

The company's dossier contained no data for immune-related AEs or specific AEs, SAEs and severe AEs for the relevant subpopulation. The information on immune-related AEs in module 4 B of the dossier refers to the total population of the KEYNOTE 045 study. The dossier also contained no data on frequent specific AEs (System Organ Class [SOC] and Preferred Term [PT]) for the relevant subpopulation. This resulted in no hint of greater or lesser harm from pembrolizumab in comparison with vinflunine; greater or lesser harm is therefore not proven for any specific AE.

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

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

Research question 1: Patients for whom cisplatin-based chemotherapy is unsuitable (first line)

The company presented insufficient data for the assessment of the added benefit of pembrolizumab as first-line therapy in patients for whom cisplatin-based chemotherapy is unsuitable. An added benefit of pembrolizumab is therefore not proven.

Research question 2: patients after pretreatment with platinum-based chemotherapy

The overall consideration only showed effects in favour of pembrolizumab for the relevant subpopulation of the KEYNOTE 045 study. These effects were shown in the outcome categories “mortality”, “morbidity” (symptoms) and “side effects”. No effects in favour or to the disadvantage of pembrolizumab were shown for the outcome “health-related quality of life”.

The dossier does not contain usable results for all patient-relevant outcomes that were investigated in the study. All results on specific AEs, particularly immune-related AEs, were only analysed for the total study population, but not for the relevant subpopulation of patients for whom, in case of allocation to the comparator arm, treatment with vinflunine had been specified prior to randomization. The alternative consideration of the results on AEs in the total population showed effects in favour of pembrolizumab (immune-related AEs and immune-related SAEs). However, based on these data it should not be assumed that the negative effects shown for the AEs in the relevant subpopulation are large enough to raise doubts about the positive effects of pembrolizumab.

In summary, there is an indication of a considerable added benefit of pembrolizumab in comparison with vinflunine for patients with locally advanced or metastatic urothelial carcinoma who had already received platinum-based chemotherapy.

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

[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: Pembrolizumab – extent and probability of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-based therapy is not an option (first line)	Chemotherapy specified by the physician	Added benefit not proven
Patients with locally advanced or metastatic urothelial carcinoma after pretreatment with a platinum-based chemotherapy	In case of early recurrence (≤ 6 months): ▪ vinflunine In case of late recurrence (> 6 to 12 months): ▪ vinflunine or ▪ repeated platinum-based chemotherapy (for patients for whom this is an option, depending on course of disease, general condition and tolerability of the first-line treatment).	Indication of considerable added benefit
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The procedure 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 pembrolizumab compared with the ACT in adult patients with locally advanced or metastatic urothelial carcinoma.

The G-BA distinguished between different patient groups in its specification of the ACT. This resulted in 2 research questions for the assessment. These are shown in Table 4.

Table 4: Research questions of the benefit assessment of pembrolizumab

Research question	**Subindication**	**ACT[a]**
1	Patients for whom cisplatin-based therapy is not an option (first line)	Chemotherapy specified by the physician
2	Patients after pretreatment with platinum-based chemotherapy	In case of early recurrence (≤ 6 months): ▪ vinflunine In case of late recurrence (> 6 to 12 months): ▪ vinflunine or ▪ repeated platinum-based chemotherapy (for patients for whom this is an option, depending on course of disease, general condition and tolerability of the first-line treatment)
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

For research question 1, the company specified carboplatin + gemcitabine to be the only relevant comparator therapy. Besides vinflunine, the company also specified paclitaxel and docetaxel as ACT for research question 2. This approach was not followed; assessment of the added benefit was conducted versus the ACT specified by the G-BA. Further reasons for this can be found in Section 2.6.1 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 Research question 1: Patients for whom cisplatin-based chemotherapy is unsuitable (first line)

2.3.1 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 pembrolizumab (status: 01/08/2017)
- bibliographical literature search on pembrolizumab (last search on 17/07/2017)
- search in trial registries for studies on pembrolizumab (last search on 18/07/2017)
- bibliographical literature search on the ACT (last search on 17/07/2017)
- search in trial registries for studies on the ACT (last search on 19/07/2017)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 29/09/2017)

Concurring with the company, the check of the completeness of the study pool produced no relevant RCTs on the direct comparison of pembrolizumab versus the ACT specified by the G-BA in adult patients with locally advanced or metastatic urothelial carcinoma.

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

Study pool of the company

The company explained that no study of direct comparison with the ACT was available for the present benefit assessment, which is why indirect comparisons had to be used as an alternative. However, according to the information provided by the company adjusted indirect comparisons with a common comparator cannot be implemented, since only one single-arm study was available for pembrolizumab in the therapeutic indication (KEYNOTE 052 [3,4]).

Therefore, the company conducted a search for studies with carboplatin + gemcitabine, since from its point of view this combination therapy is the only relevant comparator therapy for patients in the present therapeutic indication (see Section 2.6.1 of the full dossier assessment). With the help of this search, the company identified a total of 6 studies on carboplatin + gemcitabine: 4 single-arm studies as well as one study arm each from an RCT and from a retrospective study [5-11]. Detailed information on the characteristics of these studies as well as data on the interventions can be found in Appendix A.

The company presented a purely descriptive comparison of the results on pembrolizumab from the single-arm study KEYNOTE 052 with the results on carboplatin + gemcitabine from the individual study arms.

Study on pembrolizumab (KEYNOTE 052)

The KEYNOTE 052 study was a single-arm study with adult patients with locally advanced or metastatic urothelial carcinoma who had not received prior therapy for this stage of the disease and for whom cisplatin-based therapy was unsuitable. Non-eligibility for cisplatin-based treatment was defined by a poor general condition (ECOG-PS 2), kidney dysfunctions, and moderate to severe hearing loss, moderate to severe neuropathy or cardiac failure. The patients received pembrolizumab in accordance with the approval.

Studies with the combination therapy carboplatin and gemcitabine

The company included 6 studies on the combination therapy of carboplatin and gemcitabine. These included 4 single-arm studies (Bellmunt 2001, Carles 2000, Linardou 2004, Sella 2012), one individual arm of an RCT (De Santis 2012) as well as one arm of a retrospective comparison (Kim 2015). All study arms considered adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-based therapy was not an option. The criteria for the non-suitability of this therapy differ between the studies. In all studies, the basis was the general condition of the patients recorded with an ECOG-PS or WHO-PS ≥ 2 and/or a kidney dysfunction, operationalized as creatinine clearance or glomerular filtration rate ≤ 60 ml/min, partly also ≤ 50 ml/min. Three studies included age (> 75 years; Linardou 2004) or cardiac disorders (Kim 2015 and Sella 2012) as further factors.

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

The company conducted a purely descriptive comparison of study results on pembrolizumab in comparison with carboplatin + gemcitabine, which was additionally based on an incomplete data situation.

Thus, the studies on carboplatin + gemcitabine identified by the company provided only few usable data on patient-relevant outcomes. Results on overall survival were only found in 4 of the 6 studies on carboplatin + gemcitabine [6-8,10,11], none of these 6 studies included information on morbidity or health-related quality of life. The studies reported results on AEs for particular selected outcomes, which, moreover, were not identical in all studies (see module 4 A, Tables 4-98). Overall rates on SAEs, severe AEs or discontinuations due to AEs are missing in all 6 publications.

Due to the comparison of individual arms of different studies conducted by the company, the certainty of results is insufficient to derive an added benefit on this basis. The median overall survival in the KEYNOTE 052 study was 11.0 months (95% CI: [10.0; 13.6]), in the comparative studies on carboplatin + gemcitabine it ranged between 7.2 and 10 months. It cannot be excluded that an effect of this size was caused by bias alone (for one or several reasons).

Irrespective of this, the company chose carboplatin + gemcitabine as only relevant comparator therapy. The G-BA specified a therapy chosen by the physician as ACT. A detailed assessment of the comparator therapy carboplatin + gemcitabine chosen by the company can be found in Section 2.6.1 of the full benefit assessment.

In summary, usable data are not available for the assessment of pembrolizumab in adult patients with locally or metastatic urothelial carcinoma for whom cisplatin-based first-line therapy is unsuitable.

2.3.2 Results on added benefit

No suitable data are available for the derivation of an added benefit of pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma in patients for whom cisplatin-based first line treatment is unsuitable. Hence, there was no hint of an added benefit of pembrolizumab in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

The company presented insufficient data for the assessment of the added benefit of pembrolizumab as first-line therapy in patients for whom cisplatin-based chemotherapy is unsuitable. An added benefit of pembrolizumab is therefore not proven.

This assessment deviates from the approach of the company, which derived a hint of a non-quantifiable added benefit for pembrolizumab in comparison with carboplatin + gemcitabine.

2.3.4 List of included studies

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

2.4 Research question 2: patients after pretreatment with platinum-based chemotherapy

2.4.1 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 pembrolizumab (status: 01/08/2017)
- bibliographical literature search on pembrolizumab (last search on 17/07/2017)
- search in trial registries for studies on pembrolizumab (last search on 18/07/2017)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 29/09/2017)

The check identified no additional relevant study.

2.4.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab vs. vinflunine (research question 2: after platinum-based chemotherapy)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
KEYNOTE 045	Yes	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: pembrolizumab vs. chemotherapy (research question 2: after platinum-based chemotherapy)

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 045	RCT, active-controlled, open-label	Adult patients with metastatic or locally advanced urothelial carcinoma and progression or recurrence after platinum-based chemotherapy	Pembrolizumab (N = 270) Chemotherapy specified by the physician (vinflunine, paclitaxel or docetaxel[b]) (N = 272) Relevant subpopulation thereof: pembrolizumab (n = 82) Vinflunine (n = 90)	Screening: up to 42 days Treatment: until disease progression[c], complete response[d], occurrence of intolerable side effects, withdrawal of consent, decision by the investigator to discontinue, accompanying disease that inhibits further treatment, Lost to Follow-up, reaching the maximum treatment duration of 24 months[e] Observation: at least 30 days after the last treatment or until start of subsequent therapy at discontinuation of the treatment without progression up to 2 years after the end of treatment, start of a new treatment, disease progression or death	120 centres in Australia, Belgium, Chile, Denmark, France, Germany, Ireland, Israel, Italy, Japan, Canada, New Zealand, Netherlands, Norway, Austria, Peru, Poland, Portugal, Puerto Rico, Romania, Sweden, Singapore, Spain, South Korea, Taiwan, Turkey, Hungary, United Kingdom, United States 10/2014–ongoing Data cut-off 1: 1 Feb 2016[f] Data cut-off 2: 7 Sep 2016 Data cut-off 3: 18 Jan 2017	Primary: overall survival, progression-free survival Secondary: morbidity, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: The chemotherapy was chosen prior to randomization. When patients were included in the comparator arm, they received the treatment that had been specified before.
c: Under certain circumstances, treatment with pembrolizumab could also be continued beyond the occurrence of a first progression (from initial discovery of the progression until progression is confirmed in clinically stable patients).
d: Treatment could be discontinued in case of complete response, if the previous period of treatment with pembrolizumab had been at least 24 weeks and pembrolizumab had been administered at least twice after determination of the complete response; this concerned 7 (2.4%) patients in the pembrolizumab arm; in the chemotherapy group, 1 patient (0.4%) discontinued treatment after complete response.
e: under certain conditions, treatment with pembrolizumab could be restarted after further progression for at most 1 year in case of complete response or achievement of the maximum treatment duration
f: no data reported in the company's dossier.
AE: adverse event; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: pembrolizumab vs. vinflunine (research question 2: after platinum-based chemotherapy)

Study	Intervention	Comparison
KEYNOTE 045	Pembrolizumab 200 mg, every 3 weeks, intravenously	Vinflunine[a] 320 mg/m², every 3 weeks, intravenously Treatment of patients with ECOG-PS ≥ 1or ECOG-PS 0 and prior radiation of the pelvic area was initiated at a dose of 280 mg/m² in the first cycle
	Dose adjustment or interruption of treatment is possible as needed[b]	Dose adjustment or interruption of treatment is possible as needed[b]
	Prior and concomitant medication	
	Prohibited prior therapies: ▪ Other PD-1, PDL-1 or other T-cell inhibitors ▪ Anticancer monoclonal antibodies (up to 4 weeks before the start of the study) ▪ Chemotherapy with paclitaxel, docetaxel or vinflunine ▪ Other chemotherapy or radiotherapy up to 2 weeks before the start of the study Prohibited concomitant medication: ▪ Other antineoplastic systemic chemotherapies or biologics ▪ Other immunotherapies ▪ Other chemotherapies ▪ Radiation ▪ Live vaccines (up to 30 days before the start of the study) ▪ Systemic administration of glucocorticoids (only pembrolizumab arm, exception: treatment of AEs or application as premedication for one of the chemotherapies used in the study) ▪ Strong CYP3A inhibitors or inducers ▪ Drugs that prolong the QT interval (only in patients who receive vinflunine)	

a: Only the comparator therapy relevant for the assessment is presented
b: Toxicity-related dose adjustments up to treatment discontinuation were performed without relevant deviation from the requirements of the Summary of Product Characteristics (SPC).
AE: adverse event; CYP3A4: cytochrome P450 3A4; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; PD-1: programmed cell death 1 receptor; PDL-1: programmed cell death ligand 1; QTc: time interval between the start of the Q wave and the end of the T wave (corrected for heart rate); RCT: randomized controlled trial; vs.: versus

The KEYNOTE 045 study is an RCT with adult patients with locally advanced or metastatic urothelial carcinoma after platinum-based chemotherapy on/for the comparison of pembrolizumab with a chemotherapy. The investigators had the choice between vinflunine, paclitaxel and docetaxel, whereas the allocation to the respective chemotherapy had already been performed before randomization.

Treatment in both study arms was largely conducted in accordance with the respective SPCs [12,13]. Among other things, treatment in both study arms should be conducted until progression, occurrence of unacceptable side effects of the maximum treatment duration or until discontinuation of participation by investigators or patients. In the pembrolizumab arm,

treatment could also be discontinued in case of complete response, if the previous treatment period had been at least 24 weeks. Treatment of clinically stable patients with pembrolizumab could be continued at the investigator's discretion after occurrence of a first progression, until progression was confirmed after at least 4 weeks by a second examination with the help of imaging techniques. If signs for further tumour growth were absent after confirmed progression, treatment could be continued beyond this point.

Treatment duration in the pembrolizumab arm was to be at least 24 months, unless treatment had to be discontinued before due to progression, intolerance or complete response of the disease. In case of complete response or after a treatment duration of 24 months, treatment with pembrolizumab could be discontinued and then be restarted and continued for up to one year after further progression, provided there were no opposing safety concerns, the patients had not started another treatment in the meantime and the study was still ongoing. It cannot be inferred from the dossier how many patients received retreatment with pembrolizumab.

Two interim analyses were planned in the course of study. The corresponding data cut-offs were dated 1 February 2016 and 7 September 2016. The dossier contained no data for the data cut-off of 1 February 2016. According to the company, the study was stopped at the time point of the data cut-off on 07 September 2016 following a recommendation by the Data Monitoring Committee, since a statistically significant difference was shown for the outcome "overall survival". This data cut-off was the basis for the study report included in the dossier (date of the report: 14 December 2016). A further data cut-off was conducted on request of the European Medicines Agency (EMA) on 18 January 2017. In its dossier, the company presented the data cut-offs of 7 September 2016 and 18 January 2017. The latest data cut-off is relevant for the present assessment.

Patients of the chemotherapy arm could also receive follow-up treatment with pembrolizumab based on an amendment to the study protocol of 14 December 2016. According to the company, 18 patients (6.6%) of the chemotherapy arm had received pembrolizumab up to the latest data cut-off of 18 January 2017. It could be inferred from the company's approval documents that some patients in the chemotherapy arm had received pembrolizumab even before the amendment to the study protocol. Accordingly, as much as 5.1% of the patients in the chemotherapy arm had received/had been receiving pembrolizumab after progression at the time point of the data cut-off on 07 September 2016 [14].

Primary outcomes of the study were overall survival and progression-free survival. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and AEs.

Relevant subpopulation of the KEYNOTE 045 study

In the KEYNOTE 045 study, patients could also be administered paclitaxel or docetaxel besides vinflunine as a therapy option for the comparator arm of the study. However, the subpopulation relevant for the benefit assessment comprised only those patients from the pembrolizumab or comparator group who, on allocation to the comparator group, would have

or had received vinflunine. Prior to randomization, a physician chose the treatment to be given to each patient if they were allocated to the comparator group. Hence, analyses for the relevant subpopulation of the study are inherently possible without dissolution of the randomization.

In its dossier, the company presented the data for the total population of the study, but additionally conducted subgroup analyses for the characteristic "type of chemotherapy" (vinflunine, paclitaxel or docetaxel). Therefore, results on most patient-relevant outcomes are available for the relevant subpopulation. However, there were no subgroup analyses on the relevant subpopulation for any of the outcomes. Immune-related AEs and further specific AEs are exceptions, for which the company only presented data for the total population.

Altogether, the relevant subpopulation of the KEYNOTE 045 study comprises 172 of the 542 (31.7%) patients in the total population. However, vinflunine was only considered as therapeutic indication in countries where it is approved for the present therapeutic indication. Hence, it cannot be excluded that there were further patients for whom vinflunine (and not paclitaxel or docetaxel) would have been the most suitable treatment among the remaining 68.3% of the patients who were treated with taxanes. This is another reason why the results of the total population were not relevant for the present assessment.

Table 8 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: pembrolizumab vs. vinflunine (after platinum-based chemotherapy)

Study **Outcome category** **Outcome**	**Planned follow-up**
KEYNOTE 045	
Mortality	
Overall survival	after the start of a new treatment or progression of the disease every 12 weeks until death; patients who had not been reported to have died were censored at the time point of the final data cut-off
Morbidity	
Symptoms	until at most 1 year after the start of the study or until 30 days after the end of treatment, whichever occurred first
Health-related quality of life	until at most 1 year after the start of the study or until 30 days after the end of treatment, whichever occurred first
Side effects	
AEs	until 30 days after the end of treatment
SAEs	until 90 days after the end of treatment or until initiation of a subsequent therapy; then only SAEs which were considered to be associated with the treatment were reported
AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus	

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded for the period of treatment with the study medication (symptoms, health-related quality of life and AEs plus 30 days, and, for SAEs, at most 90 days or until initiation of subsequent therapy). In addition, outcomes on morbidity and health-related quality of life were recorded at most 1 year after initiation of treatment, unless treatment had been discontinued before. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Table 9 shows the characteristics of the patients in the study included (total population).

Table 9: Characteristics of the study populations – RCT, direct comparison: pembrolizumab vs. chemotherapy (research question 2: after platinum-based chemotherapy, data cut-off 18 January 2017)

Study Characteristics Category	**Pembrolizumab**	**Chemotherapy (vinflunine, paclitaxel or docetaxel)**
KEYNOTE 045	N[a] = 270	N[a] = 272
Age [years], mean (SD)	66.0 (10.2)	65.1 (9.2)
Sex [F/M], %	26/74	26/74
Ethnicity[b]		
Asian	64 (23.7)	58 (21.3)
Black or Afro-American	5 (1.9)	4 (1.5)
mixed	1 (0.4)	1 (0.4)
White	188 (69.6)	201 (73.9)
No data	12 (4.4)	6 (2.9)
Geographical region, n (%)		
EU	106 (39.3)	117 (43.0)
Non-EU	164 (60.7)	155 (57.0)
ECOG PS, n (%)		
0	120 (44.4)	106 (39.0)
1	143 (53.0)	158 (58.1)
2	2 (0.7)	4 (1.5)
Unknown	5 (1.9)	4 (1.5)
Disease stage, n (%)		
I	0 (0)	0 (0)
II	1 (0.4)	0 (0)
III	0 (0)	0 (0)
IV	269 (99.6)	272 (100)

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison: pembrolizumab vs. chemotherapy (research question 2: after platinum-based chemotherapy, data cut-off 18 January 2017) (continued)

Study Characteristics Category	Pembrolizumab	Chemotherapy (vinflunine, paclitaxel or docetaxel)
KEYNOTE 045	N[a] = 270	N[a] = 272
Extent of metastasis, n (%)		
MX	0 (0)	0 (0)
M0	6 (2.2)	8 (2.9)
M1	264 (97.8)	264 (97.1)
Presence of brain metastases, n (%)		
No	268 (99.3)	267 (98.2)
Yes	2 (0.7)	5 (1.8)
Presence of liver metastases, n (%)		
No	91 (33.7)	95 (34.9)
Yes	179 (66.3)	177 (65.1)
Time since last completed chemotherapy, n (%)		
< 3	103 (38.1)	104 (38.2)
≥ 3	167 (61.9)	168 (61.8)
Type of prior therapy		
Neoadjuvant	19 (7.0)	22 (8.1)
Adjuvant	12 (4.4)	31 (11.4)
First-line treatment	184 (68.1)	158 (58.1)
Second-line treatment	55 (20.4)	59 (21.7)
Third-line treatment	0 (0)	2 (0.7)
Haemoglobin level at the start of the study, n (%)		
< 10 g/dl	43 (15.9)	44 (16.2)
≥ 10 g/dl	219 (81.1)	224 (82.4)
Unknown	8 (3.0)	4 (1.5)
Type of chemotherapy, n (%)		
Vinflunine	82 (30.4[c])	90 (33.1[c])
Paclitaxel	94 (34.8[c])	90 (33.1[c])
Docetaxel	94 (34.8[c])	92 (33.8[c])
Treatment discontinuation, n (%)[b]	217 (81.6)	252 (98.8)
Study discontinuation, n (%)[b]	162 (60.0)	205 (75.4)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Data cut-off: 7 September 2016, data for the most recent data cut-off of 18 January 2017 are not available.
c: Institute's calculation.
EU: European Union; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The company presented no patient characteristics for the relevant subpopulation. The data for the total study population are shown here instead. Table 9 shows the proportion of EU citizens in the study population because for the considered therapeutic indication, vinflunine is only approved in the EU.

The mean age of the study participants was about 66 years, most of them were male; only about one quarter of the study population were women. Slightly more than 70% were white, nearly one quarter of the patients were from Asia. About 41% of the patients were EU residents.

In almost all patients (> 95%), the cancer had already reached the metastatic stage (stage IV), whereas stage M1 was not exceeded. Brain metastases were the exception (< 2%), however, with a share of about 66% liver metastases were frequent.

It was notable that in the chemotherapy arm, in comparison with the pembrolizumab arm, more patients received prior adjuvant treatment (11.4% in the chemotherapy arm versus 4.4% in the pembrolizumab arm) and less patients received a first-line treatment as prior therapy (58.1% in the chemotherapy arm versus 68.1% in the pembrolizumab arm).

Table 10 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab vs. chemotherapy (research question 2: after platinum-based chemotherapy, data cut-off 7 September 2016)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab**	**Vinflunine**
KEYNOTE 045	N = 82	N = 87[a]
Treatment duration [months][b]		
Median [min; max]	ND	2.10 [0.03; 12.02]
Mean (SD)	ND	3.17 (2.87)
Observation period [months]		
Overall survival, morbidity, health-related quality of life, side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a: As-treated population.
b: The median treatment duration in the total population (pembrolizumab vs. chemotherapy) amounted to 3.45 [0.03; 20.04] vs. 1.54 [0.03; 14.19] months, mean treatment duration was 5.60 (5.37) vs. 2.74 (2.71) months.
Max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The company's dossier does not provide any information on the treatment duration for the relevant study population of the KEYNOTE 045 study. The study documents present such data only for those patients in the chemotherapy arm who were treated with vinflunine, and only for the data cut-off of 7 September 2016. At this data cut-off, the median treatment duration in the pembrolizumab arm was more than twice as long as in the chemotherapy arm.

Nor does the company's documentation provide information on the observation duration for the relevant subpopulation. With the exception of the outcome "overall survival" (median observation duration: 10.3 months in the pembrolizumab arm vs. 7.9 months in the chemotherapy arm), these data are also missing for the total study population. Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: pembrolizumab vs. vinflunine (research question 2: after platinum-based chemotherapy)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
KEYNOTE 045	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the KEYNOTE 045 study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.4.2.2.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - Overall survival
- Morbidity
  - Symptoms, recorded with the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
  - Health status, recorded using the VAS of the European Quality of Life-5 Dimensions questionnaire (EQ-5D VAS)
- Health-related quality of life
  - EORTC QLQ-C30, functional scales
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - If applicable, further specific AEs

The choice of patient-relevant outcomes principally concurred with that of the company. However, the operationalization of specific AEs by the company was inadequate for the benefit assessment (see Section 2.6.2.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of the outcomes – RCT, direct comparison: pembrolizumab vs. vinflunine (research question 2: after platinum-based chemotherapy)

Study	Outcomes							
	Overall survival	Morbidity (EORTC QLQ-C30 symptom scales)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, functional scales)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Further specific adverse events
KEYNOTE 045	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]

a: No data available for the relevant subpopulation.

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; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2.2 Risk of bias

Table 13 describes the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: pembrolizumab vs. vinflunine (research question 2: after platinum-based chemotherapy)

Study		Outcomes							
	Study level	Overall survival	Morbidity (EORTC QLQ-C30 symptom scales)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs
KEYNOTE 045	L	L	H[a, b, c]	H[a, b, c]	H[a, b, c]	H[c]	H[a]	H[c]	–[d]

a: Lack of blinding.
b: Unclear how many patients actually contribute information to the analysis (see text).
c: Potentially informative censoring.
d: No data available for the relevant subpopulation.

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; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

In the KEYNOTE 045 study, there was a low risk of bias for the outcome “overall survival”. The risk of bias was high for all other outcomes included.

In the study, the outcomes on symptoms and health-related quality of life were recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30 questionnaire. The VAS of the EQ-5D questionnaire can be used for the outcome “general health status”. The high risk of bias for these patient-reported outcomes was caused by the open-label study design alone. Moreover, numerous treatment discontinuations occurred, which resulted in potentially informative censorings in the survival time analyses for these outcomes. In addition, discontinuation frequencies differed in several reasons for treatment discontinuation. Nor was information available on the number of patients for whom at least one further value was available after the start of the study. Patients for whom only one value was available at the start of the study were presumably censored immediately after the start of the study and thus provided no information for the analysis.

The high risk of bias for all outcomes on side effects also resulted from potentially informative censorings, for the outcome “discontinuation due to AEs” it could be ascribed to the open-label study design.

The assessment of the risk of bias concurs with that of the company.

In summary, at most an indication, e.g. of an added benefit, can be derived for the outcome “overall survival”, and at most a hint can be derived for the other outcomes.

2.4.2.3 Results

Table 14 summarizes the results on the comparison of pembrolizumab with vinflunine in patients with locally advanced or metastatic urothelial carcinoma who had already received platinum-based chemotherapy. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations. Kaplan-Meier curves on the outcomes analysed using survival time analyses were not available for the relevant subpopulation.

Table 14: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: pembrolizumab vs. vinflunine; research question 2: after platinum-based chemotherapy, data cut-off 18 January 2017

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Vinflunine N	Vinflunine Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. vinflunine HR [95% CI][a]; p-value[b]
KEYNOTE 045					
Mortality					
Overall survival: (18 January 2017)[c]	82	10.8 [7.4; 15.0] 54 (65.9)	90	7.4 [5.2; 8.8] 74 (82.2)	0.60 [0.41; 0.87] 0.008
Overall survival: (7 September 2016)[c]	82	10.8 [7.4; 15.2] 48 (58.5)	90	7.4 [5.2; 8.8] 66 (73.3)	0.65 [0.44; 0.96] 0.032
Morbidity					
EORTC QLQ-C30 symptom scales (Time to deterioration – 10 points)					
Fatigue	82	1.4 [0.7; 2.1] 58 (70.7)	86	1.4 [0.8; 1.4] 57 (66.3)	0.77 [0.52; 1.15] 0.200
Nausea and vomiting	82	7.0 [3.8; NA] 32 (39.0)	86	2.4 [1.9; 6.2] 37 (43.0)	0.49 [0.28; 0.85] 0.012
Pain	82	2.1 [1.5; 6.8] 43 (52.4)	86	2.1 [1.4; 3.7] 45 (52.3)	0.81 [0.52; 1.26] 0.347
Dyspnoea	82	6.2 [3.8; NA] 33 (40.2)	86	3.4 [1.5; 10.3] 38 (44.2)	0.53 [0.31; 0.90] 0.019
Insomnia	82	9.2 [2.1; NA] 32 (39.0)	86	5.3 [2.1; NA] 29 (33.7)	0.94 [0.56; 1.60] 0.862
Appetite loss	82	7.8 [4.2; NA] 32 (39.0)	86	2.4 [1.4; 3.6] 45 (52.3)	0.53 [0.32; 0.87] 0.012
Constipation	82	9.3 [4.9; NA] 27 (32.9)	86	1.6 [1.1; 3.4] 43 (50.0)	0.41 [0.24; 0.70] 0.001
Diarrhoea	82	11.8 [6.3; NA] 24 (29.3)	86	5.9 [4.0; NA] 25 (29.1)	0.79 [0.43; 1.45] 0.454
Health status (EQ-5D VAS)					
Time to deterioration – 10 points	82	4.9 [2.1; 9.2] 39 (47.6)	86	2.1 [1.5; 3.7] 42 (48.8)	0.66 [0.41; 1.06] 0.088
Time to deterioration – 7 points	82	3.7 [1.9; 7.0] 42 (51.2)	86	1.8 [1.4; 2.3] 48 (55.8)	0.64 [0.41; 1.01] 0.055

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: pembrolizumab vs. vinflunine; research question 2: after platinum-based chemotherapy, data cut-off of 18 January 2017 (continued)

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Vinflunine N	Vinflunine Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. vinflunine HR [95% CI][a]; p-value[b]
Health-related quality of life					
EORTC QLQ-C30 – functional scales (Time to deterioration – 10 points)					
Global health status/quality of life	82	3.7 [2.1; 7.0] 41 (50.0)	86	2.4 [1.6; 4.1] 40 (46.5)	0.78 [0.49; 1.26] 0.312
Physical functioning	82	2.1 [2.0; 9.0] 42 (51.2)	86	2.1 [1.4; 4.1] 44 (51.2)	0.78 [0.50; 1.22] 0.280
Role functioning	82	2.1 [1.3; 6.2] 46 (56.1)	86	1.4 [1.0; 1.6] 51 (59.3)	0.73 [0.47; 1.12] 0.151
Emotional functioning	82	7.6 [4.8; NA] 32 (39.0)	86	3.6 [2.1; 7.1] 36 (41.9)	0.65 [0.39; 1.10] 0.109
Cognitive functioning	82	4.8 [1.5; 7.6] 41 (50.0)	86	2.1 [1.4; 3.5] 42 (48.8)	0.78 [0.49; 1.25] 0.307
Social functioning	82	3.5 [2.0; 6.2] 42 (51.2)	86	1.5 [1.0; 2.4] 48 (55.8)	0.76 [0.48; 1.19] 0.227
Side effects					
AEs (supplementary information)	82	0.3 [0.2; 0.4][d] 77 (93.9)	87	0.1 [0.0; 0.1][d] 87 (100.0)	—
SAEs	82	20.0 [6.0; NA][d] 35 (42.7)	87	3.0 [0.9; NA][d] 49 (56.3)	0.56 [0.35; 0.90] 0.015
Severe AEs (CTCAE grade ≥ 3)	82	5.8 [2.1; 9.0][d] 46 (56.1)	87	0.8 [0.3; 1.4][d] 59 (67.8)	0.52 [0.34; 0.78] 0.002
Discontinuation due to AEs	82	7 (8.5)	87	13 (14.9)	RR: 0.57 [0.24; 1.36] 0.245[e]
Specific AEs					
Immune-related AEs	No data available for the relevant subpopulation				
Immune-related SAEs	No data available for the relevant subpopulation				
Immune-related severe AEs (CTCAE grade ≥ 3)	No data available for the relevant subpopulation				
Further specific AEs	No data available for the relevant subpopulation				

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: pembrolizumab vs. vinflunine; research question 2: after platinum-based chemotherapy, data cut-off of 18 January 2017 (continued)

a: Cox proportional hazards model stratified by Eastern Cooperative Oncology Group Performance Status [ECOG PS] (0/1 vs. 2), presence of liver metastases (yes vs. no), haemoglobin level (≥ 10 g/dl vs. < 10 g/dl) and time since last completed chemotherapy (< 3 months vs. ≥ 3 months).
b: Two-sided p-value (Wald test).
c: The added benefit was derived on the basis of the data cut-off of 18 January 2017; the data cut-off of 7 September 2016 was presented as additional information.
d: Module 4 B shows the median time to event in weeks; for reasons of clarity, the weeks were converted into months based on the Institute's calculation.
e: Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [15]).
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome "overall survival", and at most hints for all other outcomes. Further explanation can be found in Section 2.4.2.2.

Mortality

Overall survival

A statistically significant difference in favour of pembrolizumab was shown for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab in comparison with vinflunine for this outcome.

This concurs with the company's assessment, which also derived an indication of an added benefit, however, on the basis of the total study population, and not of the relevant subpopulation.

Morbidity

Symptoms, recorded using the symptom scales of the EORTC QLQ-C30

Statistically significant differences between the treatment groups in favour of pembrolizumab were shown for the outcomes "nausea and vomiting", "dyspnoea", "loss of appetite" and "constipation". The effect shown for the outcome "dyspnoea" was no more than marginal, which resulted in no hint of an added benefit. For the outcomes "nausea and vomiting", "loss of appetite" and "constipation", there was a hint of an added benefit of pembrolizumab in comparison with vinflunine.

There were no statistically significant differences between the treatment groups for the outcomes "fatigue", "pain", "insomnia" and "diarrhoea". Hence, there was no hint of an

added benefit of pembrolizumab in comparison with vinflunine; an added benefit for these outcomes is therefore not proven.

This assessment deviates from that of the company, which overall found a hint of an added benefit for the disease symptoms, however, based on the total study population and thus on further subscales, for which no statistically significant difference was shown for the relevant subpopulation.

Health status, recorded using the EQ-5D VAS

There was no statistically significant difference between the treatment arms for the outcome "health status", irrespective of whether deterioration is based on a threshold value of 10 or 7 points. This resulted in no hint of an added benefit of pembrolizumab in comparison with vinflunine; an added benefit is therefore not proven for this outcome.

This deviates from the company's assessment, which also derived a hint of an added benefit, however, on the basis of the total study population, and not of the relevant subpopulation.

Health-related quality of life

EORTC QLQ-C30, functional scales

A statistically significant difference between the treatment groups was not shown for any of the functional scales of the EORTC QLQ-C30. This resulted in no hint of an added benefit of pembrolizumab in comparison with vinflunine; an added benefit is therefore not proven for the outcome "health-related quality of life".

This deviates from the company's assessment, which also derived a hint of an added benefit, however, on the basis of the total study population, and not of the relevant subpopulation.

Side effects

SAEs

A statistically significant difference in favour of pembrolizumab was shown for the outcome "SAEs". This resulted in a hint of lesser harm from pembrolizumab in comparison with vinflunine for this outcome.

This concurs with the company's assessment, however, on the basis of the total study population and not of the relevant subpopulation.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of pembrolizumab was shown for the outcome "severe AEs". This resulted in a hint of lesser harm from pembrolizumab in comparison with vinflunine for this outcome.

This concurs with the company's assessment, however, on the basis of the total study population and not of the relevant subpopulation.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab in comparison with vinflunine; greater or lesser harm is therefore not proven for this outcome.

This deviates from the company's assessment, which also derived a hint of an added benefit, however, on the basis of the total study population, and not of the relevant subpopulation.

Immune-related AEs and further specific AEs

The company's dossier contained no data on immune-related AEs or specific SAEs and severe AEs for the relevant subpopulation. The information on immune-related AEs in module 4 B of the dossier refers to the total population of the KEYNOTE 045 study. The dossier also contained no data on frequent specific AEs (SOC and PT) for the relevant subpopulation. This resulted in no hint of greater or lesser harm from pembrolizumab in comparison with vinflunine; greater or lesser harm is therefore not proven for any specific AE.

Appendix B shows an overview of the common AEs, SAEs, severe AEs, discontinuations due to AEs and immune-related AEs for the total study population.

2.4.2.4 Subgroups and other effect modifiers

The company's dossier includes subgroup analyses only for the total population of the KEYNOTE 045 study, but not for the relevant subpopulation. An analysis of possible effect modifiers is therefore not possible.

2.4.3 Probability and extent of added benefit

The probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The procedure for deriving an overall conclusion on the added benefit based on the aggregation of conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 resulted in indications and hints of an added benefit or lesser harm. The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Determination of the outcome category for the outcomes on symptoms (EORTC QLQ-C30)

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-severe/non-serious or severe/serious. The classification of these outcomes is justified below.

Since it could not be inferred from the dossier that the outcomes “nausea and vomiting”, “dyspnoea”, “loss of appetite” and “constipation” (symptoms) of the EORTC QLQ-C30 were severe or serious symptoms, these outcomes were allocated to the outcome category of non-serious/non-severe symptoms/late complications. This classification deviated from the assessment of the company, which rated the outcomes “dyspnoea” and “constipation” as being severe/serious.

Table 15: Extent of added benefit at outcome level: pembrolizumab vs. vinflunine; research question 2: after platinum-based chemotherapy (data cut-off of 18 January 2017)

Outcome category **Outcome**	**Pembrolizumab vs. vinflunine** **Median time to event** **or** **Proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	10.8 vs. 7.4 months HR: 0.60 [0.41; 0.87]; p = 0.008 Probability: "indication"	Outcome category: "mortality" $0.85 \leq CI_u < 0.95$ Added benefit, extent: "considerable"
Morbidity		
Symptoms		
EORTC QLQ-C30 symptom scales – time to deterioration[c]		
Fatigue	1.4 vs. 1.4 months HR: 0.77 [0.52; 1.15]; p = 0.200	Lesser benefit/added benefit not proven
Nausea and vomiting	7.0 vs. 2.4 months HR: 0.49 [0.28; 0.85]; p = 0.012 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Pain	2.1 vs. 2.1 months HR: 0.81 [0.52; 1.26]; p = 0.347	Lesser benefit/added benefit not proven
Dyspnoea	6.2 vs. 3.4 months HR: 0.53 [0.31; 0.90][d] p = 0.019	Outcome category non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Insomnia	9.2 vs. 5.3 months HR: 0.94 [0.56; 1.60]; p = 0.862	Lesser benefit/added benefit not proven
Appetite loss	7.8 vs. 2.4 months HR: 0.53 [0.32; 0.87]; p = 0.012 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Constipation	9.3 vs. 1.6 months HR: 0.41 [0.24; 0.70]; p = 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Added benefit, extent: "considerable"
Diarrhoea	11.8 vs. 5.9 months HR: 0.79 [0.43; 1.45]; p = 0.454	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS) – time to deterioration		
Responder criterion 10 points	4.9 vs. 2.1 months HR: 0.66 [0.41; 1.06]; p = 0.088	Lesser benefit/added benefit not proven
Responder criterion 7 points	3.7 vs. 1.8 months HR: 0.64 [0.41; 1.01]; p = 0.055	

(continued)

Table 15: Extent of added benefit at outcome level: pembrolizumab vs. vinflunine; research question 2: after platinum-based chemotherapy (data cut-off of 18 January 2017) (continued)

Outcome category **Outcome**	**Pembrolizumab vs. vinflunine** **Median time to event** **or** **Proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30, functional scales – time to deterioration		
Global health status/quality of life	3.7 vs. 2.4 months HR: 0.78 [0.49; 1.26]; p = 0.312	Lesser benefit/added benefit not proven
Physical functioning	2.1 vs. 2.1 months HR: 0.78 [0.50; 1.22]; p = 0.280	Lesser benefit/added benefit not proven
Role functioning	2.1 vs. 1.4 months HR: 0.73 [0.47; 1.12]; p = 0.151	Lesser benefit/added benefit not proven
Emotional functioning	7.6 vs. 3.6 months HR: 0.65 [0.39; 1.10]; p = 0.109	Lesser benefit/added benefit not proven
Cognitive functioning	4.8 vs. 2.1 months HR: 0.78 [0.49; 1.25]; p = 0.307	Lesser benefit/added benefit not proven
Social functioning	3.5 vs. 1.5 months HR: 0.76 [0.48; 1.19]; p = 0.227	Lesser benefit/added benefit not proven
Side effects		
SAEs	87.1 vs. 13.1 weeks HR: 0.56 [0.35; 0.90][d] p = 0.015 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)	25.4 vs. 3.3 weeks HR: 0.52 [0.34; 0.78]; p = 0.002 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Discontinuation due to AEs	8.5% vs. 14.9% RR: 0.57 [0.24; 1.36]; p = 0.245	Greater/lesser harm not proven
Specific AEs		
Immune-related AEs	No data available for the relevant subpopulation	
Immune-related SAEs	No data available for the relevant subpopulation	
Immune-related severe AEs (CTCAE grade ≥ 3)	No data available for the relevant subpopulation	
Further specific AEs	No data available for the relevant subpopulation	

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_o.
c: The time to deterioration by at least 10 points is presented.
d: Detailed information on the upper limit of the CI is not available, therefore it is assumed to be ≥ 0.90 for the purposes of the benefit assessment.
e: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

(continued)

Table 15: Extent of added benefit at outcome level: pembrolizumab vs. vinflunine; research question 2: after platinum-based chemotherapy (data cut-off of 18 January 2017) (continued)

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of pembrolizumab in comparison with vinflunine (research question 2: after platinum-based chemotherapy)

Positive effects	**Negative effects**
Mortality ▪ Overall survival: indication of an added benefit – extent: "considerable"	–
Non-serious/non-severe symptoms/late complications ▪ Nausea and vomiting: hint of an added benefit – extent: "minor" ▪ Loss of appetite: hint of an added benefit – extent "minor" ▪ Constipation: hint of an added benefit – extent "considerable"	–
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "minor" ▪ Severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent "considerable"	–
No results on immune-related side effects and further specific AEs available for the relevant subpopulation.	
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

The overall consideration only showed effects in favour of pembrolizumab for the relevant subpopulation of the KEYNOTE 045 study. These effects were shown in the outcome categories "mortality", "morbidity" (symptoms) and "side effects". No effects in favour or to the disadvantage of pembrolizumab were shown for the outcome "health-related quality of life".

The dossier does not contain usable results for all patient-relevant outcomes that were investigated in the study. All results on specific AEs, particularly immune-related AEs, were only analysed for the total study population, but not for the relevant subpopulation of patients for whom, in case of allocation to the comparator arm, treatment with vinflunine had been specified prior to randomization. Additional consideration of the results on AEs in the total population showed effects to the disadvantage of pembrolizumab (immune-related AEs and

immune-related SAEs). However, based on these data it should not be assumed that the negative effects shown for the AEs in the relevant subpopulation are large enough to raise doubts about the positive effects of pembrolizumab.

In summary, there is an indication of a considerable added benefit of pembrolizumab in comparison with vinflunine for patients with locally advanced or metastatic urothelial carcinoma who had already received platinum-based chemotherapy.

The assessment described above deviates from that of the company, which assumed an indication of a major added benefit.

2.4.4 List of included studies

KEYNOTE 045

Bellmunt J, De Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017; 376(11): 1015-1026.

Merck Sharp & Dohme. A phase III randomized clinical trial of pembrolizumab (MK-3475) versus paclitaxel, docetaxel or vinflunine in subjects with recurrent or progressive metastatic urothelial cancer [online]. In: Clinical Trials Peruvian Registry. [Accessed: 04.10.2017]. URL: http://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=074-14.

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Merck Sharp & Dohme. A study of pembrolizumab (MK-3475) versus paclitaxel, docetaxel, or vinflunine for participants with advanced urothelial cancer (MK-3475-045/KEYNOTE-045): full text view [online]. In: ClinicalTrials.gov. 31 August 2017 [Accessed: 04.10.2017]. URL: https://ClinicalTrials.gov/show/NCT02256436.

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MSD Sharp & Dohme. A phase III randomized clinical trial of pembrolizumab (MK-3475) versus paclitaxel, docetaxel or vinflunine in subjects with recurrent or progressive metastatic urothelial cancer: study MK-3475-045; clinical study report [unpublished]. 2016.

MSD Sharp & Dohme. A phase III randomized clinical trial of pembrolizumab (MK-3475) versus paclitaxel, docetaxel or vinflunine in subjects with recurrent or progressive metastatic urothelial cancer; study MK-3475-045; Zusatzauswertung [unpublished]. 2017.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 17.

Table 17: Pembrolizumab – extent and probability of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-based therapy is not an option (first line)	Chemotherapy specified by the physician	Added benefit not proven
Patients with locally advanced or metastatic urothelial carcinoma after pretreatment with a platinum-based chemotherapy	In case of early recurrence (≤ 6 months): ▪ vinflunine In case of late recurrence (> 6 to 12 months): ▪ vinflunine or ▪ repeated platinum-based chemotherapy (for patients for whom this is an option, depending on course of disease, general condition and tolerability of the first-line treatment).	Indication of considerable added benefit
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The procedure for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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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