IQWiG Reports – Commission No. A21-34

Pembrolizumab (urothelial carcinoma first-line treatment) –

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 Erstlinientherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2021). 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
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NYHA	New York Heart Association
PD-L1	programmed cell death ligand 1
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary 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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 March 2021.

The limitation was set because the data available for the previous assessment were based on incomplete data from the comparison of individual arms from different studies. For the new benefit assessment after expiry of the deadline, the study results on all patient-relevant outcomes from the currently ongoing KEYNOTE 361 study were to be submitted in the dossier.

Research question

The aim of the present report was to assess the added benefit of pembrolizumab in comparison with chemotherapy specified by the physician as appropriate comparator therapy (ACT) for the treatment of locally advanced or metastatic urothelial carcinoma in adult patients who are not eligible for cisplatin-containing chemotherapy and whose tumours express programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 10.

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a]
Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10	Chemotherapy specified by the physician[b]
a. Presentation of the respective ACT specified by the G-BA. b. The combination therapy from carboplatin and gemcitabine is a suitable comparator. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

The company specified carboplatin + gemcitabine to be the only relevant comparator therapy. The combination therapy of carboplatin + gemcitabine is not approved for the present therapeutic indication.

Regarding the ACT "chemotherapy specified by the physician", the G-BA added the comment that the combination therapy of carboplatin + gemcitabine was a suitable comparator. Study results with comparative data versus carboplatin + gemcitabine were used for the assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Study pool and study design

The RCT KEYNOTE 361 was included for the assessment of the added benefit. This study compares pembrolizumab with a chemotherapy of either cisplatin + gemcitabine or carboplatin + gemcitabine.

The study included adult patients with treatment-naive advanced or metastatic urothelial carcinoma and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 2.

Treatment with pembrolizumab was in compliance with the Summary of Product Characteristics (SPC). Treatment with carboplatin + gemcitabine corresponded to the specifications of Appendix VI (off-label use) to Section K of the Pharmaceutical Directive.

Primary outcomes of the KEYNOTE 361 study were overall survival and progression-free survival. Further outcomes were recorded in the outcome categories “morbidity”, “health-related quality of life” and “adverse events (AEs)”.

The company presented analyses of a subpopulation of the KEYNOTE 361 study whose tumours express PD-L1 with a CPS ≥ 10 and for whom cisplatin-based therapy is not considered suitable. This subpopulation relevant for the benefit assessment comprised 56 patients in the pembrolizumab arm and 64 patients in the chemotherapy arm. The patients in the chemotherapy arm of the subpopulation received treatment with carboplatin + gemcitabine.

The median treatment duration of the patients in the pembrolizumab arm was 4.2 months, in the chemotherapy arm it was 3.7 months.

Risk of bias

The risk of bias across outcomes (study level) was rated as low for the KEYNOTE 361 study. The outcome-specific risk of bias was rated as low for the outcomes “overall survival” and "severe AEs” and as high for all other outcomes for which usable data were available.

Results

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

Morbidity

European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (symptom scales)

Fatigue, nausea and vomiting, pain, insomnia, constipation

No statistically significant difference between the treatment groups was shown for any of the following outcomes: fatigue, nausea and vomiting, pain, insomnia, and constipation. In each case, this resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

Shortage of breath

No statistically significant difference between the treatment groups was shown for the outcome "shortage of breath". There was an effect modification by the characteristic “age”, however. This resulted in a hint of minor added benefit from pembrolizumab in comparison with chemotherapy specified by the physician for the outcome “shortage of breath” in patients ≥ 65 years. For patients < 65 years of age, this resulted in no hint of an added benefit of pembrolizumab in comparison with a chemotherapy specified by the physician; an added benefit is therefore not proven.

Appetite loss

A statistically significant difference to the disadvantage of pembrolizumab was shown between the treatment groups for the outcome “appetite loss”. However, the extent of the effect for this outcome of the category “non-serious/non-severe symptoms/late complications” was no more than marginal. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

Diarrhoea

No statistically significant difference between the treatment groups was shown for the outcome "diarrhoea". There was an effect modification by the characteristic “sex”. This resulted in a hint of minor added benefit from pembrolizumab in comparison with chemotherapy specified by the physician for the outcome “diarrhoea” in women. For men, this resulted in no hint of an added benefit of pembrolizumab in comparison with a chemotherapy specified by the physician; an added benefit is therefore not proven.

Health status, recorded with the EQ-5D visual analogue scale (VAS)

The dossier contained no usable data for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. In each case, this resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". There was an effect modification by the characteristic “age”, however. This resulted in a hint of lesser harm from pembrolizumab in comparison with chemotherapy specified by the physician for the outcome “SAE” in patients < 65 years. For patients ≥ 65 years of age, this resulted in no hint of lesser or greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician; lesser or greater harm is therefore not proven.

Severe adverse events (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome “severe AEs (CTCAE grade ≥ 3)”. This resulted in an indication of lesser harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of lesser or greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician; lesser or greater harm is therefore not proven.

Immune-related SAEs, immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment groups was shown for each of the outcomes "immune-related SAEs” and "immune-related severe AEs (CTCAE grade ≥ 3)”. In each case, this resulted in no hint of lesser or greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician; lesser or greater harm is therefore not proven.

Gastrointestinal disorders (AEs)

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome “gastrointestinal disorders”. This resulted in a hint of lesser harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

Blood and lymphatic system disorders (severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome "blood and lymphatic system disorders (severe AEs [CTCAE grade ≥ 3])". This resulted in an indication of lesser harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

Metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome "metabolism and nutrition disorders (severe AEs [CTCAE grade ≥ 3])". This resulted in a hint of greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

Vascular disorders (severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome "vascular disorders (CTCAE grade ≥ 3)". This resulted in a hint of greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

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:

The overall consideration showed both positive and negative effects for pembrolizumab versus a chemotherapy specified by the physician.

The advantages arise in particular in the outcome category "serious/severe AEs" due to an indication of lesser harm with the extent: "major". In addition, there are hints of a minor added benefit in the category of non-serious/non-severe symptoms/late complications, as well as hints of a lower harm in the categories of serious/severe side effects and non-serious/non-severe side effects. These are contrasted by hints of greater harm in the serious/severe AEs. These negative effects do not completely challenge the indication of a positive effect in the serious/severe side effects.

In summary, there is an indication of a considerable added benefit of pembrolizumab in comparison with chemotherapy specified by the physician for patients with locally advanced or

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

metastatic urothelial carcinoma who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a CPS ≥ 10.

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

Table 3: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10	Chemotherapy specified by the physician	Indication of considerable added benefit[b]
a. Presentation of the respective ACT specified by the G-BA. b. The added benefit exists only in comparison with carboplatin + gemcitabine, which is assessed as sufficiently suitable comparator by the G-BA (see Section 2.2). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for the derivation of 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 the present report was to assess the added benefit of pembrolizumab in comparison with chemotherapy specified by the physician as ACT for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT[a]**
Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10	Chemotherapy specified by the physician[b]
a. Presentation of the respective ACT specified by the G-BA. b. The combination therapy from carboplatin and gemcitabine is a suitable comparator. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

The company specified carboplatin + gemcitabine to be the only relevant comparator therapy. As already described in the dossier assessments A17-46 [3] and A18-89 [4], the combination therapy of carboplatin + gemcitabine is not approved for the present therapeutic indication [5,6].

In its justification on the first assessment, the G-BA explained that, in the present therapeutic indication, it saw a sufficient medical reason in this special treatment and health care situation that exceptionally justified taking data from a comparison with carboplatin + gemcitabine into account [7]. Regarding the ACT "chemotherapy specified by the physician", the G-BA added the comment that the combination therapy of carboplatin + gemcitabine was a suitable comparator [8]. Therefore, study results with comparative data versus carboplatin + gemcitabine were also used for the assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

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 list on pembrolizumab (status: 1 March 2021)
- bibliographical literature search on pembrolizumab (last search on 25 January 2021)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 1 February 2021)
- search on the G-BA website for pembrolizumab (last search on 2 February 2021)

The completeness of the study pool was checked by:

- search in trial registries for studies on pembrolizumab (last search on 8 April 2021); for search strategies, see Appendix D of the full dossier assessment.

The check did not identify any additional relevant study.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
KEYNOTE 361	Yes	Yes	No	No[c]	Yes [9,10]	No

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool concurs with that of the company.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab vs. characteristics of the included study – RCT, direct comparison: pembrolizumab vs. chemotherapy specified by the physician

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 361	RCT, open-label, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed locally advanced or metastatic urothelial carcinoma with an ECOG PS ≤ 2, without prior systemic chemotherapy[b]	Pembrolizumab (N = 307) chemotherapy[c] (N = 352) pembrolizumab + chemotherapy[d] (N = 351) relevant subpopulation thereof[e]: pembrolizumab (n = 56) carboplatin + gemcitabine (N = 64)	Screening: up to 42 days before start of treatment treatment: until complete remission, disease progression, unacceptable toxicity or reaching the maximum duration of therapy (24 months for pembrolizumab) observation[f]: outcome-specific, at most until death, withdrawal of consent or end of study	172 centres in Argentina, Belgium, Brazil, Canada, Chile, France, Germany, Hungary, Ireland, Israel, Japan, Korea, Netherlands, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, United Kingdom, USA 09/2016–ongoing data cut-offs: 12 July 2018 (interim analysis 1) 19 March 2019 (interim analysis 2) 29 April 2020 (final analysis)	Primary: overall survival, progression-free survival secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Related to a locally advanced or metastatic urothelial carcinoma.
c. Cisplatin + gemcitabine or carboplatin + gemcitabine, choice of the platinum component before randomization.
d. The arm is not relevant for the assessment and is no longer presented in the following tables.
e. The patients met the following criteria: assignment to carboplatin and PD-L1-expressing tumour (CPS ≥ 10) and not eligible for treatment with cisplatin according to the criteria described in Section 2.3.2.
f. Outcome-specific information is provided in Table 8.

AE: adverse event; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: relevant subpopulation; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine

Study	Intervention	Comparison
KEYNOTE 361	Pembrolizumab 200 mg IV every 3 weeks, for a maximum of 24 months (35 cycles)	Carboplatin area under the curve (AUC) 5ml/min[a], IV, every 3 weeks + gemcitabine 1000 mg/m² body surface areas (BSA), IV, on day 1 and 8 of a 3-week cycle
	Permitted pretreatment ▪ neoadjuvant platinum-based chemotherapy with recurrence > 12 months after completion of the therapy ▪ adjuvant platinum-based chemotherapy after radical cystectomy with recurrence > 12 months after completion of the therapy **non-permitted pretreatment** ▪ monoclonal antibodies for direct antineoplastic treatment within 4 weeks before the first dose of study treatment (6 weeks for nitrosoureas or mitomycin C) ▪ anti-PD-1, anti-PD-L1, or anti-PD-L2 agents or agents directed against another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137) ▪ allogeneic stem cell or bone marrow transplantation ▪ systemic therapies (disease-modifying drugs, corticosteroids, immunosuppressants) for an active autoimmune disorder in the last 2 years ▪ other investigational preparations within 4 weeks before first dose of study medication ▪ systemic steroids and immunosuppressants (within 7 days before randomization) ▪ live vaccine within the last 30 months before study inclusion **permitted concomitant treatment** ▪ any treatment necessary for the patient's wellbeing	

a. Or AUC 4.5 ml/min, if required by local guidelines.

AUC: area under the curve; BSA: body surface area; IV: intravenous; PD-1: programmed cell death 1; PD-L1/PD-L2: programmed cell death ligand 1/2; RCT: randomized controlled trial

KEYNOTE 361 is an ongoing, open-label, multicentre RCT comparing pembrolizumab with chemotherapy of either cisplatin + gemcitabine or carboplatin + gemcitabine. Another treatment arm, in which pembrolizumab was administered in combination with chemotherapy, is not relevant for the assessment and is not considered hereinafter.

The study included adult patients with treatment-naive advanced or metastatic urothelial carcinoma and an ECOG PS of ≤ 2. The PD-L1 expression of the tumour tissue was examined in a central laboratory during the screening phase. Information on the used test was not available in Module 4 A of the dossier.

Patients were stratified by PD-L1 expression (CPS ≥ 10 vs. CPS < 10) and randomly assigned to the pembrolizumab arm (N = 307) or the chemotherapy arm (N = 352). The investigator chose of the platinum component for the chemotherapy prior to randomization.

Treatment with pembrolizumab corresponds to the specifications of the SPCs [11]. Treatment was planned for up to 35 therapy cycles (24 months). Patients who had stable disease or a complete or partial response after completion of the therapy could be treated with pembrolizumab for up to 17 additional cycles. Patients who had discontinued pembrolizumab after at least 8 cycles when stable disease was achieved could also resume treatment with pembrolizumab for up to an additional 17 cycles in the event of progression.

The therapy of carboplatin + gemcitabine is not approved for patients who are not eligible for cisplatin-based therapy. However, the German S3 guideline [12] recommends the therapy with carboplatin + gemcitabine in the present therapy situation and, with a decision date of 20 May 2021, is likely to be prescribable in the future according to Annex VI (off-label use) Pharmaceutical Directive [13]. The treatment regimen with carboplatin + gemcitabine used in KEYNOTE 361 is largely in compliance with the specifications of the Pharmaceutical Directive. In the Pharmaceutical Directive, 4 to 6 therapy cycles are usually assumed. The information in Module 4 A shows that carboplatin + gemcitabine could be administered for up to 9 cycles, but the median treatment duration was 3.7 months (approx. 5 to 6 cycles). Patients in the chemotherapy arm were eligible for follow-up therapy with pembrolizumab after disease progression (as determined by Response Evaluation Criteria in Solid Tumours [RECIST] criteria version 1.1). This is a use according to the approval.

Primary outcomes of the KEYNOTE 361 study were overall survival and progression-free survival. Patient-relevant secondary outcomes were recorded in the categories of morbidity, health-related quality of life and AEs.

Relevant subpopulation

Only a subpopulation of the KEYNOTE 361 study is relevant for answering the present research question. These are patients with locally advanced or metastatic urothelial carcinoma whose tumours express PD-L1 with a CPS ≥ 10 and for whom cisplatin-based therapy is unsuitable. The company presented analyses of a subpopulation of the KEYNOTE 361 study for whom cisplatin-based therapy is considered unsuitable due to at least one of the following criteria [12]:

- ECOG performance status ≥ 2 or Karnofsky performance status ≤ 70%
- creatinine clearance < 60 mL/min
- hearing loss in audiometry ≥ grade 2
- peripheral neuropathy ≥ 2
- cardiac failure according to New York Heart Association (NYHA) class > III

This subpopulation presented by the company is relevant for the benefit assessment comprised 56 patients in the pembrolizumab arm and 64 patients in the chemotherapy arm. The patients

in the chemotherapy arm of the subpopulation received treatment with carboplatin + gemcitabine.

Data cut-offs

Data are available on 3 data cut-offs:

- First data cut-off of 12 July 2018: preplanned interim analysis
- Second data cut-off of 18 March 2019: preplanned interim analysis
- Third data cut-off of 29 April 2020: preplanned final analysis

In Module 4 A, the company presented the results of the final data cut-off. These data serve as the basis for the benefit assessment.

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine

Study **outcome category** **outcome**	**Planned follow-up observation**
KEYNOTE 361	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30)	Until treatment discontinuation, at most until week 27 (control arm) or week 102 (intervention arm)
Health status (EQ-5D VAS)	Until treatment discontinuation, at most until week 27 (control arm) or week 102 (intervention arm)
Health-related quality of life (EORTC QLQ-C30)	Until treatment discontinuation, at most until week 27 (control arm) or week 102 (intervention arm)
Side effects	
AEs, severe AEs[a]	30 days after the last dose of the study medication
SAEs	90 days after the last dose of study medication (when switching to a subsequent therapy, the follow-up observation period might be reduced to 30 days)
a. Severe AEs are operationalized as CTCAE grade ≥ 3.	
AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” are systematically shortened. For instance, the outcomes of the category “AEs“ were only recorded for the period of treatment with the study medication plus 30 days (AEs and

severe AEs) or up to 90 days (for SAEs). The outcomes of the categories “morbidity” and “health-related quality of life” were observed until discontinuation of treatment. 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 relevant subpopulation of the study included.

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine (multipage table)

Study characteristic category	**Pembrolizumab N[a] = 56**	**Carboplatin + gemcitabine N[a] = 63**
KEYNOTE 361		
Age [years], mean (SD)	71 (8)	73 (8)
Sex [F/M], %	25/75	27/73
Family origin, n (%)		
Asian	7 (13)	19 (30)
Black or African American	1 (2)	0 (0)
White	36 (64)	37 (59)
Unknown	12 (21)	7 (11)
ECOG PS, n (%)		
0	16 (29)	29 (46)
1	30 (54)	25 (40)
2	10 (18)	9 (14)
Extent of metastasis, n (%)		
M0	3 (5)	7 (11)
M1	53 (95)	56 (89)
Location of metastases, n (%)		
Lymph nodes only	17 (30)	20 (32)
Visceral metastases	38 (68)	41 (65)
No lymph nodes or visceral metastases	1 (2)	2 (3)
Liver metastases, n (%)		
No	45 (80)	55 (87)
Yes	11 (20)	8 (13)
Location of primary tumour, n (%)		
Upper urinary tract	12 (21)	19 (30)
Lower urinary tract	44 (79)	44 (70)
Baseline haemoglobin, n (%)		
< 10 g/dL	9 (16)	5 (8)
≥ 10 g/dL	47 (84)	58 (92)
Prior adjuvant or neoadjuvant platinum-based chemotherapy		
No	53 (95)	56 (89)
Yes	3 (5)	7 (11)

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine (multipage table)

Study characteristic category	Pembrolizumab N[a] = 56	Carboplatin + gemcitabine N[a] = 63
Reason to choose carboplatin		
Age	0 (0)	1 (2)
Poor performance status	2 (4)	2 (3)
Cardiac failure	0 (0)	0 (0)
Predisposition for nausea and vomiting	0 (0)	2 (3)
Presence of a neuropathy	0 (0)	0 (0)
Relevant hearing impairment	3 (5)	3 (5)
Renal insufficiency	40 (71)	46 (73)
Other	0 (0)	0 (0)
Several	8 (14)	9 (14)
Not applicable	3 (5)	0 (0)
Treatment discontinuation, n (%)	45 (80)	32 (52)
Study discontinuation, n (%)	40 (71)	50 (79)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely comparable between the treatment arms. The mean age of the patients was about 72 years, most of them were male; only about one quarter of were women. Slightly more than 60% were of white family origin, the proportion of patients of Asian family origin was only about half as large in the intervention arm than in the comparator arm (13% vs. 30%). Slightly more than 65% of the patients already had visceral metastases, about 30% only had metastases in the lymph nodes. In about 70% of the patients, the choice of carboplatin as component of the combination chemotherapy was due to renal insufficiency.

Transferability to the German health care context

According to the company, the results of the KEYNOTE 361 study can be transferred to the German health care context due to the characteristics of the investigated patient population, the study design and the approval-compliant use of pembrolizumab.

The company did not provide any further information on the transferability of the study results to the German health care context.

Information on the course of the study

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. carboplatin + gemcitabine

Study **duration of the study phase** **outcome category**	**Pembrolizumab** **N = 56**	**Carboplatin + gemcitabine** **N = 63**
KEYNOTE 361		
Treatment duration [months]		
Median [min; max]	4.2 [ND; ND]	3.7 [ND; ND]
Mean (SD)	ND	ND
Observation period[a] [months]		
Overall survival		
Median [min; max]	14.5 [ND; ND]	12.1 [ND; ND]
Mean (SD)	ND	ND
Morbidity, health-related quality of life (EQ-5D/EORTC QLQ-C30)		
Median [min; max]	5.5 [ND; ND]	4.5 [ND; ND]
Mean (SD)	ND	ND
Side effects		
AEs		
Median [min; max]	5.2 [ND; ND]	4.7 [ND; ND]
Mean (SD)	ND	ND
SAEs		
Median [min; max]	7.1 [ND; ND]	6.7 [ND; ND]
Mean (SD)	ND	ND

a. The company did not provide any information on the determination of observation periods.

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation

The median treatment and observation periods only differed marginally between the study arms.

Information on subsequent therapies

Table 11 shows which subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine (KEYNOTE 361)

Study **drug class** **drug**	**Patients with subsequent therapy n (%)**	
	pembrolizumab N = 56	**carboplatin + gemcitabine N = 63**
KEYNOTE 361		
First subsequent therapy[a, b]		
Total	18 (32)	37 (59)
Anti-PD1/PD-L1 therapies	0 (0)	23 (62)
Pembrolizumab	0 (0)	15 (41)
Durvalumab	0 (0)	4 (11)
Atezolizumab	0 (0)	3 (8)
Nivolumab	0 (0)	1 (3)
Other	18 (100)	14 (38)
Gemcitabine	16 (89)	6 (16)
Carboplatin	13 (72)	4 (11)
Cisplatin	5 (28)	1 (3)
Methotrexate	1 (6)	3 (8)
Paclitaxel	1 (6)	2 (5)
Doxorubicin	1 (6)	1 (3)
Vinblastine sulphate	1 (6)	1 (3)
Epirubicin	0 (0)	1 (3)
Inhibitor of the fibroblast growth factor receptor (unspecified)	0 (0)	1 (3)
Investigational preparation (unspecified)	0 (0)	1 (3)
Nedaplatin	0 (0)	1 (3)
Rogaratinib	0 (0)	1 (3)
Tegafur (+) uracil	0 (0)	1 (3)

a. No information on further subsequent therapies.
b. Own calculation of the percentages of the presented follow-up therapies in relation to patients with (at least) 1 follow-up therapy after discontinuation of the study medication.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Overall, 18 (32%) patients in the pembrolizumab arm and 37 (59%) patients in the carboplatin + gemcitabine arm had received a subsequent therapy until the final data cut-off of 29 April 2020. For almost all patients in the pembrolizumab arm, the subsequent therapy consisted of a platinum-based combination chemotherapy with gemcitabine. In the carboplatin + gemcitabine arm, 41% of the patients who received subsequent therapy were administered pembrolizumab.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE 361	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the KEYNOTE 361 study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the EORTC QLQ-C30 symptom scales
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related AEs (SAEs and severe AEs)

- further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows for which outcomes data were available in the study included.

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine

Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs and severe AEs[a]	Further specific AEs[a, b]
KEYNOTE 361	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events were considered (MedDRA coding): "gastrointestinal disorders (SOC, AEs)", "blood and lymphatic system disorders (SOC, severe AEs)", "metabolism and nutrition disorders (SOC, severe AEs)" and "vascular disorders (SOC, severe AEs)".
a. No usable data available; see following text for reasons.

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; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on analyses of the outcome categories "morbidity" and "health-related quality of life"

- Symptoms and health-related quality of life: In its dossier, the company presented responder analyses for the symptom scales or the functional scales of the EORTC QLQ-C30 for the time to first deterioration by 10 points (respective scale range 0 to 100). As explained in the *General Methods* of the Institute ([1,14]), for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). For the EORTC QLQ-C30 and its additional modules, the analysis with a previously accepted response threshold of 10 points is considered a

sufficient approximation to an analysis with a 15% threshold (15 points) in certain constellations and is used for the benefit assessment (for explanation see [15]). Regardless of this, analyses with the previously accepted response threshold of 10 points for the EORTC QLQ-C30 as well as all additional modules of the EORTC will primarily be used for a transitional period until the adjusted module templates for the dossier come into force (siehe FAQs des G-BA [16]).

- Health status: The outcome "health status" was recorded with the EQ-5D VAS. The responder analyses are not used for the dossier assessment because the response criteria used (time to first deterioration by ≥ 7 or 10 points [scale range 0-100]) do not correspond to at least 15% of the scale range on a predefined basis, nor to exactly 15% of the scale range on a post hoc basis. The responder analyses used by the company are presented as supplementary information in Appendix C of the full dossier assessment.

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine

Study	Study level	Outcomes								
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs and severe AEs	Further specific AEs[a, b]
KEYNOTE 361	N	N	H[c, d, e]	–[f]	H[c, d, e]	H[d]	N	H[c]	H[d]	H[c, d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events were considered (MedDRA coding): “gastrointestinal disorders (SOC, AEs)”, “blood and lymphatic system disorders (SOC, severe AEs)”, “metabolism and nutrition disorders (SOC, severe AEs)” and “vascular disorders (SOC, severe AEs)“.
c. Lack of blinding in subjective recording of outcomes or subjective decosopm for treatment discontinuation; in case of the specific AEs, this applies to the non-severe and the non-serious AEs.
d. Incomplete observations for potentially informative reasons.
e. Strong decrease in response rates over the course of the study.
f. No usable data available; for reasons, see Section 2.4.1 of the present dossier assessment.

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; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the result on the outcome “overall survival” was rated as low. This concurs with the company's assessment.

For the outcomes on symptoms (symptom scales of EORTC QLQ-C30) and on health-related quality of life (functional scales of the EORTC QLQ-C30), the risk of bias of the results was rated as high each due to the lack of blinding in subjective recording of outcomes. Further reasons for this classification for the outcomes on symptoms and health-related quality of life are, on the one hand, that the returns of the questionnaires strongly decreased in the course of the study. On the other hand, the planned measurements, which were repeated over time, were incomplete for a significant proportion of patients for potentially informative reasons (such as treatment discontinuation due to progression). The company also cited the latter as a further reason for a high risk of bias.

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS (see Section 2.4.1). For this reason, the risk of bias for this outcome was not assessed. This deviates from the assessment of the company, which used the outcome “health status recorded with the EQ-5D VAS” for the assessment and assumed a high risk of bias for it.

For the outcome “severe AEs (CTCAE grade ≥ 3)”, the risk of bias of the result was rated as low: On the one hand, events occurred in a large proportion of patients (approx. 73% of patients in the intervention arm and approx. 89% of patients in the comparator arm), and in the majority of these patients they occurred at an early time point in the course of the study. On the other hand, censoring did not occur to a relevant extent in the first months, in which the Kaplan-Meier curves already showed discrepancies (Figure 21). Therefore, there is no increased risk of bias in the estimated hazard ratio due to potentially informative censoring. The assessment of the risk of bias concurs with that of the company.

Due to incomplete observation for potentially informative reasons, the risk of bias is rated as high for the outcomes “SAEs”, “immune-related SAEs”, “immune-related severe AEs” as well as “specific AEs”; for “non-serious/non-severe AEs”, the risk of bias is also rated as high due to the lack of blinding. This deviates from the assessment of the company, which rated the risk of bias of these outcomes as low.

Deviating from the company's assessment, the risk of bias was rated as high for the outcome "discontinuation due to AEs". This was justified with the lack of blinding in subjective decision for treatment discontinuation.

Despite a high risk of bias due to the very early occurrence of the events in the comparator arm and the resulting clear difference in the Kaplan-Meier curves (Figure 26), it is not assumed that the shortened observation periods for potentially informative reasons call the observed effects in the specific AE “blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), into question. Hence, a high certainty of results is assumed for this outcome despite the

high risk of bias, so that at most an indication, e.g. of an added benefit, can be determined for this outcome.

2.4.3 Results

Table 15 summarizes the results for the comparison of pembrolizumab with carboplatin + gemcitabine in patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a CPS ≥ 10. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the event time analyses are presented in Appendix A. The results on the common AEs, SAEs and severe AEs, as well as on all AEs that led to treatment discontinuation are presented in Appendix B of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine (multipage table)

Study outcome category outcome	Pembrolizumab		Carboplatin + gemcitabine		Pembrolizumab vs. carboplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
KEYNOTE 361					
Mortality					
Overall survival	56	14.5 [8.0; 18.0] 40 (71.4)	63	12.1 [8.5; 19.2] 49 (77.8)	0.93 [0.61; 1.42]; 0.740
Morbidity					
EORTC QLQ-C30 – symptom scales[b]					
Fatigue	50	1.4 [0.8; 2.1] 36 (72.0)	55	1.4 [0.9; 4.1] 33 (60.0)	1.10 [0.67; 1.80]; 0.697
Nausea and vomiting	50	8.1 [4.2; NC] 18 (36.0)	55	NA [2.4; NC] 20 (36.4)	0.74 [0.37; 1.50]; 0.406
Pain	50	2.3 [0.9; 10.4] 28 (56.0)	55	4.1 [2.1; NC] 24 (43.6)	1.33 [0.75; 2.34]; 0.327
Shortage of breath	50	8.9 [2.1; NC] 20 (40.0)	55	3.7 [1.6; NC] 28 (50.9)	0.64 [0.35; 1.17]; 0.151
Insomnia	50	9.0 [6.3; NC] 19 (38.0)	55	NA [4.7; NC] 13 (23.6)	0.99 [0.45; 2.17]; 0.976
Appetite loss	50	3.9 [1.4; 7.9] 28 (56.0)	55	6.1 [6.1; NC] 17 (30.9)	1.92 [1.04; 3.55]; 0.038
Constipation	50	8.1 [2.4; NC] 19 (38.0)	55	NA [1.4; NC] 21 (38.2)	0.85 [0.45; 1.61]; 0.626
Diarrhoea	50	NA [8.3; NC] 13 (26.0)	55	NA [4.7; NC] 17 (30.9)	0.63 [0.29; 1.36]; 0.239
Health status (EQ-5D VAS)	No usable data[c]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine (multipage table)

Study outcome category outcome	Pembrolizumab		Carboplatin + gemcitabine		Pembrolizumab vs. carboplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30 – functional scales[b]					
Global health status	50	5.3 [2.1; 8.1] 28 (56.0)	55	4.1 [1.4; NC] 29 (52.7)	0.74 [0.42; 1.30]; 0.294
Physical functioning	50	3.5 [0.8; 5.3] 32 (64.0)	55	3.1 [1.4; NC] 29 (52.7)	1.09 [0.64; 1.85]; 0.748
Role functioning	50	2.0 [0.8; 6.8] 30 (60.0)	55	1.9 [1.4; NC] 30 (54.5)	1.10 [0.65; 1.86]; 0.728
Emotional functioning	50	NA [2.4; NC] 14 (28.0)	55	NA [4.4; NC] 14 (25.5)	1.18 [0.55; 2.52]; 0.669
Cognitive functioning	50	5.1 [2.2; 18.4] 24 (48.0)	55	2.2 [1.4; NC] 28 (50.9)	0.70 [0.40; 1.25]; 0.232
Social functioning	50	3.5 [1.4; 6.8] 30 (60.0)	55	4.4 [1.7; NC] 24 (43.6)	1.23 [0.70; 2.17]; 0.478
Side effects[d]					
AEs (supplementary information)	55	0.6 [0.2; 0.7] 53 (96.4)	62	0.2 [0.1; 0.3] 62 (100.0)	–
SAEs	55	4.9 [3.1; NC] 30 (54.5)	62	NA [3.1; NC] 25 (40.3)	1.24 [0.72; 2.14]; 0.431
Severe AEs[e]	55	3.6 [1.9; 5.3] 40 (72.7)	62	1.1 [0.7; 1.9] 55 (88.7)	0.36 [0.23; 0.58]; < 0.001
Discontinuation due to AEs	55	NA 11 (20.0)	62	NA 7 (11.3)	1.32 [0.48; 3.63]; 0.597
Immune-related SAEs	55	NA 3 (5.5)	62	NA 0 (0)	NC; 0.052
Immune-related severe AEs[e]	55	NA 4 (7.3)	62	NA 1 (1.6)	3.56 [0.37; 34.19]; 0.272
Specific AEs					
Gastrointestinal disorders (SOC, AEs)	55	5.6 [2.3; 8.0] 30 (54.5)	62	0.9 [0.3; 1.6] 44 (71.0)	0.39 [0.23; 0.64]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine (multipage table)

Study outcome category outcome	Pembrolizumab		Carboplatin + gemcitabine		Pembrolizumab vs. carboplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
Blood and lymphatic system disorders (SOC, severe AEs[e])	55	NA 9 (16.4)	62	2.1 [1.4; 2.6] 49 (79.0)	0.13 [0.06; 0.27][f]; < 0.001[g]
Metabolism and nutrition disorders (SOC, severe AEs[e])	55	NA 11 (20.0)	62	NA 4 (6.5)	3.40 [1.08; 10.67][f]; 0.036[g]
Vascular disorders (SOC, severe AEs[e])	55	NA 5 (9.1)	62	NA 0 (0)	ND[f, h] 0.029[g]

a. Unless otherwise stated, effect and CI based on an unstratified Cox proportional hazards model with associated p-value based on Wald test statistics or score test in case of 0 events in one of the study arms.
b. Time to deterioration, defined as an increase in score by ≥ 10 points (for the symptom scales) or a decrease in score by ≥ 10 points (for the functional scales) in comparison with baseline; scale range: 0-100 points.
c. No usable data available; for reasons, see Section 2.4.1.
d. The company excluded the MedDRA terms "“neoplasm progression", "malignant neoplasm progression" and "disease progression" from the analysis of side effects.
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. Effect and CI: unstratified Cox proportional hazards model with CI according to Wald. The results tables of the company show that it used the penalised likelihood method according to Firth for specific severe AEs (CTCAE grade ≥ 3) if the p-value did not match the observed data. It remains unclear how the non-compliance assumed by the company was operationalized and in which outcomes such a case occurred. It is also unclear whether the company also used this method for outcomes other than specific severe AEs (CTCAE grade ≥ 3).
g. p-value: 2-sided Wald test or score test in case of 0 events in a treatment group. The results tables of the company show that it used the penalised likelihood method according to Firth for specific severe AEs (CTCAE grade ≥ 3) if the p-value did not match the observed data. It remains unclear how the non-compliance assumed by the company was operationalized and in which outcomes such a case occurred. It is also unclear whether the company also used this method for outcomes other than specific severe AEs (CTCAE grade ≥ 3).
h. Underlying model for effect estimation unclear. An effect estimation of the HR is possible if the p-value is based on the penalised likelihood method.

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; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most indications can be determined for the outcomes “overall survival”, “severe AEs (CTCAE grade ≥ 3)” and “blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3])”, and at most hints, e.g. of an added benefit, can be determined for all other outcomes.

With regard to the results for the outcome categories “morbidity”, “health-related quality of life” and “side effects”, it should be noted that due to the strongly different planned maximum treatment durations in the two study arms, the hazard ratio (HR) only reflects approximately the first 6 months of the study course.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Morbidity

The company did not perform an outcome-specific derivation of the added benefit for the outcomes of the category “morbidity”, but considered the added benefit as not proven across all outcomes. Hence, the company’s outcome-specific assessment is not described below.

EORTC QLQ-C30 (symptom scales)

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales.

Fatigue, nausea and vomiting, pain, insomnia, constipation

No statistically significant difference between the treatment groups was shown for any of the following outcomes: fatigue, nausea and vomiting, pain, insomnia, and constipation. In each case, this resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

Shortage of breath

No statistically significant difference between the treatment groups was shown for the outcome "shortage of breath". However, there was an effect modification by the characteristic “age” (see Section 2.4.4). This resulted in a hint of minor added benefit from pembrolizumab in comparison with chemotherapy specified by the physician for the outcome “shortage of breath” in patients ≥ 65 years. For patients < 65 years of age, this resulted in no hint of an added benefit of pembrolizumab in comparison with a chemotherapy specified by the physician; an added benefit is therefore not proven.

Appetite loss

A statistically significant difference to the disadvantage of pembrolizumab was shown between the treatment groups for the outcome “appetite loss”. However, the extent of the effect for this outcome of the category “non-serious/non-severe symptoms/late complications” was no more

than marginal. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

Diarrhoea

No statistically significant difference between the treatment groups was shown for the outcome "diarrhoea". However, there was an effect modification by the characteristic “sex” (see Section 2.4.4). This resulted in a hint of minor added benefit from pembrolizumab in comparison with chemotherapy specified by the physician for the outcome “diarrhoea” in women. For men, this resulted in no hint of an added benefit of pembrolizumab in comparison with a chemotherapy specified by the physician; an added benefit is therefore not proven.

Health status recorded using the EQ-5D VAS

There were no usable analyses for the outcome "health status" recorded with the EQ-5D VAS (see Section 2.4.1). This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life was recorded with the EORTC QLQ-C30 functional scales.

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. In each case, this resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Side effects

The company did not conduct an outcome-specific derivation of the added benefit for the outcomes of the category “side effects”, but derived an indication of an added benefit across all outcomes. Hence, the company’s outcome-specific assessment is not described below.

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". However, there was an effect modification by the characteristic “age” (see Section 2.4.4). This resulted in a hint of lesser harm from pembrolizumab in comparison with chemotherapy specified by the physician for the outcome “SAE” in patients < 65 years. For patients ≥ 65 years of age, this resulted in no hint of lesser or greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician; lesser or greater harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in an indication of lesser harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of lesser or greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician; lesser or greater harm is therefore not proven.

Immune-related SAEs, immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment groups was shown for each of the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)". In each case, this resulted in no hint of lesser or greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician; lesser or greater harm is therefore not proven.

Gastrointestinal disorders (AEs)

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome "gastrointestinal disorders". This resulted in a hint of lesser harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

Blood and lymphatic system disorders (severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome "blood and lymphatic system disorders (severe AEs [CTCAE grade ≥ 3])". This resulted in an indication of lesser harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

Metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome "metabolism and nutrition disorders (severe AEs [CTCAE grade ≥ 3])". This resulted in a hint of greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

Vascular disorders (severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of pembrolizumab in comparison with carboplatin + gemcitabine was shown for the outcome "vascular disorders (severe AEs [CTCAE grade ≥ 3])". A quantification of the extent was not possible as there is no effect estimation for this outcome. This resulted in a hint of greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- ECOG PS in the screening phase (0/1 vs. 2)

In Module 4 A, the company presents analyses on a number of potential effect modifiers, some of which, however, only refer to the outcome "overall survival". According to the dossier templates of the G-BA, the investigation of effect modifiers was required across all available outcomes. In Module 4 A, for instance, the subgroup analyses reflecting the characteristic "disease severity", such as the characteristic "Bajorin risk factor (0 vs. 1 vs. 2)" [12], are incomplete. In order to be still able to assess the impact of disease severity on the outcomes available in the KEYNOTE 361 study, the subgroup analyses on ECOG PS (0/1 vs. 2) were used.

Moreover, the company did not present any subgroup analyses for the prespecified outcomes "immune-related SAEs" and "immune-related severe AEs" in Module 4 A of the dossier, so that a possible impact of effect modifiers on these outcomes cannot be assessed.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 shows the results of the subgroup analyses. Kaplan-Meier curves on the event time analyses on the subgroups are presented in Appendix A of the full dossier assessment.

Table 16: Subgroups (morbidity, side effects) – RCT, direct comparison: pembrolizumab vs. carboplatin + gemcitabine

Study outcome characteristic Subgroup	Pembrolizumab N	Pembrolizumab median time to event in months [95 % CI] patients with event n (%)	Carboplatin + gemcitabine N	Carboplatin + gemcitabine median time to event in months [95 % CI] patients with event n (%)	Pembrolizumab vs. carboplatin + gemcitabine HR [95% CI][a]	 p-value[a]
KEYNOTE 361						
Morbidity						
Symptoms (EORTC QLQ-C30 symptom scales)[b]						
Shortage of breath						
Age (years)						
< 65	13	1.8 [0.7; NC] 7 (53.8)	11	NA [0.7; NC] 3 (27.3)	2.60 [0.67; 10.12]	0.168
≥ 65	37	8.9 [7.9; NC] 13 (35.1)	44	2.4 [1.5; 4.3] 25 (56.8)	0.41 [0.20; 0.86]	0.018
Total					Interaction[c]:	0.027
Diarrhoea						
Sex						
Male	37	NA [4.2; NC] 11 (29.7)	42	NA [4.7; NC] 10 (23.8)	1.08 [0.44; 2.61]	0.869
Female	13	12.8 [12.8; NC] 2 (15.4)	13	1.6 [0.8; NC] 7 (53.8)	0.10 [0.01; 0.82]	0.032
Total					Interaction[c]:	0.035
Side effects						
SAEs						
Age						
< 65	12	23.9 [0.6; NC] 5 (41.7)	11	1.0 [0.1; 3.7] 9 (81.8)	0.30 [0.09; 0.97]	0.044
≥ 65	43	4.8 [3.1; NC] 25 (58.1)	51	NA 16 (31.4)	1.89 [0.999; 3.58]	0.050
Total					Interaction[c]:	0.002

a. Effect, CI and p-value are based on an unstratified Cox proportional hazards model with corresponding Wald test statistics.
g. Time to deterioration; defined as an increase in score by ≥ 10 points in comparison with baseline; scale range: 0-100.
c. Likelihood ratio test from Cox proportional hazards model with corresponding interaction term; unstratified.

AE: adverse event; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event

Morbidity

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

Shortage of breath

There was an effect modification by the characteristic "age" for the outcome "shortage of breath". There was no statistically significant difference between the treatment arms for patients < 65 years. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + pembrolizumab was shown for patients ≥ 65 years". This resulted in a hint of a added benefit of pembrolizumab in comparison with a chemotherapy specified by the physician.

Diarrhoea

There was an effect modification by the characteristic "sex" for the outcome "diarrhoea". For men, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the chemotherapy specified by the physician; an added benefit is therefore not proven.

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + gemcitabine was shown for women. This resulted in a hint of a added benefit of pembrolizumab in comparison with a chemotherapy specified by the physician.

Side effects

SAEs

There was an effect modification by the characteristic "age" for the outcome "SAEs". There was no statistically significant difference between the treatment arms for patients ≥ 65 years of age. This resulted in no hint of lesser or greater harm from pembrolizumab in comparison with a chemotherapy specified by the physician; lesser or greater harm is therefore not proven.

A statistically significant difference in favour of pembrolizumab in comparison with carboplatin + gemcitabine was shown for patients < 65 years". This resulted in a hint of lesser harm from pembrolizumab in comparison with a chemotherapy specified by the physician.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below. taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification for these outcomes is justified.

Module 4 A did not provide any information on the classification of the severity category for the outcomes “shortage of breath”, “appetite loss” and “diarrhoea” recorded with the EORTC QLQ-C30 symptom scales. Therefore, these outcomes were assigned to the outcome category of non-serious/non-severe symptoms.

Table 17: Extent of added benefit at outcome level: pembrolizumab vs. chemotherapy specified by the physician (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab vs. chemotherapy specified by the physician** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 14.5 vs. 12.1 months HR: 0.93 [0.61; 1.42]; p = 0.740	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC-QLQ-C30 symptom scales – deterioration by ≥ 10 points)		
Fatigue	Median: 1.4 vs. 1.4 months HR: 1.10 [0.67; 1.80]; p = 0.697	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 8.1 months vs. NA HR: 0.74 [0.37; 1.50]; p = 0.406	Lesser benefit/added benefit not proven
Pain	Median: 2.3 vs. 4.1 months HR: 1.33 [0.75; 2.34]; p = 0.327	Lesser benefit/added benefit not proven
Shortage of breath Age < 65 years	Median: 1.8 months vs. NA HR: 2.60 [0.67; 10.12]; p = 0.168	Lesser benefit/added benefit not proven
≥ 65 years	Median: 8.9 vs. 2.4 months HR: 0.41 [0.20; 0.86]; p = 0.018 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: “minor”
Insomnia	Median: 9.0 months vs. NA HR: 0.99 [0.45; 2.17]; p = 0.976	Lesser benefit/added benefit not proven
Appetite loss	Median: 3.9 vs. 6.1 months HR: 1.92 [1.04; 3.55] HR: 0.52 [0.28; 0.96][c]; p = 0.038	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Constipation	Median: 8.1 months vs. NA HR: 0.85 [0.45; 1.61]; p = 0.626	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab vs. chemotherapy specified by the physician (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab vs. chemotherapy specified by the physician** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Diarrhoea		
Sex Male	Median: NA vs. NA HR: 1.08 [0.44; 2.61]; p = 0.869	Lesser benefit/added benefit not proven
Female	Median: 12.8 vs. 1.6 months HR: 0.10 [0.01; 0.82]; p = 0.032 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: “minor”
Health status (EQ-5D VAS)	No usable data[e]	
Health-related quality of life		
Symptoms (EORTC-QLQ-C30 functional scales – deterioration by ≥ 10 points)		
Global health status	Median: 5.3 vs. 4.1 months HR: 0.74 [0.42; 1.30]; p = 0.294	Lesser benefit/added benefit not proven
Physical functioning	Median: 3.5 vs. 3.1 months HR: 1.09 [0.64; 1.85]; p = 0.748	Lesser benefit/added benefit not proven
Role functioning	Median: 2.0 vs. 1.9 months HR: 1.10 [0.65; 1.86]; p = 0.728	Lesser benefit/added benefit not proven
Emotional functioning	Median: NA vs. NA HR: 1.18 [0.55; 2.52]; p = 0.669	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 5.1 vs. 2.2 months HR: 0.70 [0.40; 1.25]; p = 0.232	Lesser benefit/added benefit not proven
Social functioning	Median: 3.5 vs. 4.4 months HR: 1.23 [0.70; 2.17]; p = 0.478	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab vs. chemotherapy specified by the physician (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab vs. chemotherapy specified by the physician** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs Age < 65 years	Median: 23.9 vs. 1.0 months HR: 0.30 [0.09; 0.97]; p = 0.044 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: “minor”
≥ 65 years	Median: 4.8 months vs. NA HR: 1.89 [0.999; 3.58]; p = 0.050	Greater/lesser harm not proven
Severe AEs	Median: 3.6 vs. 1.1 months HR: 0.36 [0.23; 0.58]; p < 0.001 probability: "indication”	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5 % lesser harm, extent: "major"
Discontinuation due to AEs	Median: NA vs. NA HR: 1.32 [0.48; 3.63]; p = 0.597	Greater/lesser harm not proven
Immune-related SAEs	Median: NA vs. NA HR: -[f]; p = 0.052	Greater/lesser harm not proven
Immune-related severe AEs	Median: NA vs. NA HR: 3.56 [0.37; 34.19]; p = 0.272	Greater/lesser harm not proven
Gastrointestinal disorders (AEs)	Median: 5.6 vs. 0.9 months HR: 0.39 [0.23; 0.64]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: “considerable”
Blood and lymphatic system disorders (severe AEs)	Median: NA vs. 2.1 months HR: 0.13 [0.06; 0.27]; p < 0.001 probability: "indication”[g]	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5 % lesser harm, extent: "major"
Metabolism and nutrition disorders (severe AEs)	Median: NA vs. NA HR: 3.40 [1.08; 10.67] HR: 0.29 [0.09; 0.93][c]; p = 0.036 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”

Table 17: Extent of added benefit at outcome level: pembrolizumab vs. chemotherapy specified by the physician (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab vs. chemotherapy specified by the physician** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Vascular disorders (severe AEs)	Median: NA vs. NA HR: ND[h] ; p = 0.029 probability. “hint”	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. See Section 2.4.1 of the present dossier assessment for reasons.
f. Meaningful estimation of HR impossible with the method used (score test method) (no event in the control arm).
g. The certainty of results is considered high, as the observation of such a large effect is not explicable by incomplete observations for potentially informative reasons alone.
h. Underlying model for effect estimation unclear. An effect estimation of the HR is possible if the p-value is based on the penalised likelihood method (see Table 15).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; NA: not achieved; ND: not data; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of pembrolizumab compared with chemotherapy specified by the physician

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications[a] ▪ shortage of breath ▫ age (≥ 65 years): hint of added benefit – extent: "minor" ▪ diarrhoea ▫ sex (women): hint of an added benefit – extent: "minor"	-
Serious/severe side effects[a] ▪ SAEs: ▫ age (< 65 years): hint of lesser harm – extent: "minor" ▪ severe AEs: indication of lesser harm – extent: "major" including ▫ blood and lymphatic system disorders: indication of lesser harm – extent: "major"	Serious/severe side effects[a] ▪ metabolism and nutrition disorders (severe AEs): hint of greater harm – extent: "minor" ▪ vascular disorders (severe AEs): hint of greater harm – extent: "non-quantifiable"
Non-serious/non-severe side effects[a] ▪ gastrointestinal disorders: hint of lesser harm – extent: "considerable"	-
When interpreting the results it should be noted that due to the strongly different planned maximum treatment durations in the study arms, HR only reflects approximately the first 6 months of the study course. AE: adverse event; SAE: serious adverse event	

The overall consideration showed both positive and negative effects for pembrolizumab versus a chemotherapy specified by the physician.

The advantages arise in particular in the outcome category "serious/severe AEs" due to an indication of lesser harm with the extent: "major". In addition, there are hints of a minor added benefit in the category of non-serious/non-severe symptoms/late complications, as well as hints of a lower harm in the categories of serious/severe side effects and non-serious/non-severe side effects. These are contrasted by hints of greater harm in the serious/severe AEs. These negative effects do not completely challenge the indication of a positive effect in the serious/severe side effects.

In summary, there is an indication of a considerable added benefit of pembrolizumab in comparison with chemotherapy specified by the physician for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a CPS ≥ 10.

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 19.

Table 19: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10	Chemotherapy specified by the physician	Indication of considerable added benefit[b]
a. Presentation of the respective ACT specified by the G-BA. d. The added benefit exists only in comparison with carboplatin + gemcitabine, which is assessed as sufficiently suitable comparator by the G-BA (see Section 2.2). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of non-quantifiable added benefit.

The approach for the derivation of 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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