IQWiG Reports – Commission No. A21-23

Avelumab (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 *Avelumab (Urothelkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 May 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Avelumab (urothelial carcinoma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
18 February 2021

Internal Commission No.
A21-23

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

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Keywords: Avelumab, Urologic Neoplasms, Carcinoma – Transitional Cell, Benefit Assessment, NCT02603432

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abkürzung	Bedeutung
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
DRS-E	Disease-Related Symptoms Subscale - Emotional
DRS-P	Disease-Related Symptoms Subscale - Physical
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions visual analogue scale
FDA	U. S. Food and Drug Administration
FWB	Functional Wellbeing
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NFBlSI-18	NCCN/FACT Bladder Symptom Index-18
PD-L1	programmed cell death ligand 1
PT	Preferred Term
RCT	Randomized controlled Trial (randomisierte kontrollierte Studie)
RECIST	Response Evaluation Criteria in Solid Tumours
RKI	Robert Koch Institute
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TSE	Treatment Side Effects
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 avelumab. 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 18 February 2021.

Research question

The aim of the present report was to assess the added benefit of avelumab as first-line maintenance therapy in combination with best supportive care (BSC) (hereinafter referred to as "avelumab + BSC") in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 2.

Table 2: Research questions of the benefit assessment of avelumab + axitinib

Research question	Therapeutic indication	ACT[a]
1	Adults with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy	BSC[b]

a. Presentation of the respective ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

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. This concurs with the company's inclusion criteria.

Study pool and study design

The study JAVELIN Bladder 100 was used for the benefit assessment.

The JAVELIN Bladder 100 study is an ongoing, open-label, randomized, controlled multicentre study on the comparison of avelumab + BSC with BSC. The study included adult patients with unresectable, locally advanced or metastatic stage IV urothelial carcinoma who were

progression-free following platinum-based first-line chemotherapy. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients with ECOG PS > 1 and active brain metastases were excluded from participation in the study; hence, no data are available for them.

Overall, 700 patients were randomly allocated either to treatment with avelumab + BSC (N = 350) or to BSC (N = 350) in a 1:1 ratio. Randomization was stratified according to the degree of best response to first-line induction chemotherapy (complete or partial response vs. stable disease) and localization of metastases (visceral vs. non-visceral). Treatment with avelumab was implemented without relevant deviations from the specifications of the Summary of Product Characteristics (SPC).

Primary outcome of the JAVELIN Bladder 100 study was overall survival in the total population and the prespecified programmed cell death ligand 1 (PD-L1)-positive subpopulation. For the benefit assessment, the company analysed the data only for the total population; in its analyses, it considered the PD-L1 status as a subgroup. The outcomes on symptoms, health status and adverse events (AEs) were recorded as patient-relevant secondary outcomes.

Results are available for 2 data cut-offs (first data cut-off: 21 October 2019; second data cut-off: 19 January 2020). The second data cut-off was recorded as part of the approval by the U. S. Food and Drug Administration (FDA) and represents a 90-day safety update to the first data cut-off. In the dossier, the company only evaluates the data of the first data cut-off in detail. As there are only minor differences in the results of the outcomes on overall survival and side effects between the two data cut-offs, the first data cut-off is used for the present benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for the JAVELIN Bladder 100 study.

The risk of bias for the results of the outcome "overall survival" at outcome level was rated as low. For the results of all other outcomes, the risk of bias was rated as high.

Based on the available data, at most an indication, e.g. of an added benefit, can be derived for the outcome “overall survival”, and at most hints for all other outcomes due to the high risk of bias.

Results

Mortality

Overall survival

The JAVELIN Bladder 100 study showed a statistically significant difference between the treatment groups in favour of avelumab + BSC for the outcome “overall survival”. This resulted in an indication of an added benefit of avelumab + BSC in comparison with BSC.

Morbidity

Symptoms (Disease-Related Symptoms Subscale – Physical [DRS-P])

There was no statistically significant difference between the treatment groups for the outcome "symptoms", recorded using the DRS-P subscale of the NCCN/FACT Bladder Symptom Index-18 (NFBISI-18) questionnaire. This resulted in no hint of an added benefit of avelumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Symptoms (Treatment Side Effects [TSE])

There was no statistically significant difference between the treatment groups for the outcome "symptoms", recorded using the TSE subscale of the NFBISI-18 questionnaire. This resulted in no hint of an added benefit of avelumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS])

There was no statistically significant difference between the treatment groups for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of avelumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

In the JAVELIN Bladder 100 study, no outcome suitable to reflect the health-related quality of life was recorded. This resulted in no hint of an added benefit of avelumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

There was no statistically significant difference between the treatment arms for the outcome "SAEs". This resulted in no hint of greater or lesser harm from avelumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference between the treatment groups to the disadvantage of avelumab + BSC was shown for the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)". As a result, there was a hint of greater harm of avelumab + BSC in comparison with BSC.

Discontinuation due to AEs

There were no usable data for discontinuation due to AEs. This resulted in no hint of greater or lesser harm from avelumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Specific AEs

Immune-related AEs and infusion-related reactions

There are no usable data for the outcomes "immune-related AEs" and "infusion-related reactions". This resulted in no hint of greater or lesser harm from avelumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Hypothyroidism (Preferred Term [PT], AEs), gastrointestinal disorders (System Organ Class [SOC], AEs), infections and infestations (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs) lipase increased (PT, severe AEs [CTCAE grade ≥ 3]), amylase increased (PT, severe AEs [CTCAE grade ≥ 3]), metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of avelumab + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcomes mentioned. This resulted in a hint of greater harm from avelumab + BSC in comparison with BSC.

Arthralgia (PT, AEs)

A statistically significant difference between the treatment groups to the disadvantage of avelumab + BSC in comparison with BSC was shown for the outcome "arthralgia (PT, AEs)". Moreover, there was an effect modification by the characteristic "age". For patients ≥ 65 years of age, there was a hint of greater harm from avelumab + BSC in comparison with BSC. For patients < 65 years of age, there was no hint of greater or lesser harm from avelumab + BSC in comparison with BSC; greater or lesser harm for patients < 65 years of age is therefore not proven.

Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference between the treatment groups in favour of avelumab + BSC in comparison with BSC was shown for the outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)" (SOC, severe AEs [CTCAE grade ≥ 3])". This resulted in a hint of greater harm from avelumab + BSC in comparison with BSC.

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

Based on the results presented, probability and extent of the added benefit of the drug avelumab in comparison with the ACT are assessed as follows:

[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

For avelumab + BSC in comparison with BSC, the overall consideration showed both positive and negative effects of different extents and with different probabilities (indication or hint). These relate both to the outcome "overall survival" and to outcomes on side effects of different severity grades.

As a positive effect, an indication of a considerable added benefit of avelumab + BSC in comparison with BSC could be determined for the outcome “overall survival”.

For side effects with different severity grades, both positive and negative effects of different extents, each with the probability “hint”, were shown for avelumab + BSC in comparison with BSC. However, these were increasingly to the disadvantage of avelumab + BSC. Greater harm with the extent “major” was found for the outcome “severe AEs”. The remaining effects only occurred in individual specific AEs. For the outcome "neoplasms benign, malignant and unspecified (incl. cysts and polyps)" in the category "serious/severe AEs" alone, lesser harm with the extent "minor” can be assumed for avelumab + BSC in comparison with BSC. However, it is questionable whether the positive effect for the outcome “neoplasms benign, malignant and unspecified (incl cysts and polyps)” should actually be allocated to the outcome category “side effects” or whether it rather reflects the symptoms of the disease. Clear demarcation not possible on the basis of the available information.

Since the negative effects do not completely challenge the positive effect for the outcome “overall survival”, an indication of a minor added benefit of avelumab over BSC can be derived for adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free after platinum-based first-line chemotherapy.

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

Table 3: Avelumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy	BSC	Indication of minor added benefit[b]
a. Presentation of the respective ACT specified by the G-BA. b. Almost only patients with an ECOG PS of 0 or 1 were included in the JAVELIN Bladder 100 study. Patients with active brain metastases were excluded. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with active brain metastases. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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].

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 avelumab as first-line maintenance therapy in combination with the ACT in adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 4.

Table 4: Research questions of the benefit assessment of avelumab

Research question	Therapeutic indication	ACT[a]
1	Adults with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy	BSC[b]

a. Presentation of the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

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 avelumab (status: 18 January 2021)
- bibliographical literature search on avelumab (last search on 18 January 2021)
- search in trial registries/trial results databases for studies on avelumab (last search on 18 January 2021)
- search on the G-BA website for avelumab (last search on 18 January 2021)

To check the completeness of the study pool:

- search in trial registries for studies on avelumab (last search on 2 March 2021)

The check did not identify any additional relevant studies.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: avelumab + BSC vs. BSC

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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
JAVELIN Bladder 100	Yes	Yes	No	No[d]	Yes [3-5]	Yes [6,7]

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. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. 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.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the present benefit assessment of avelumab + BSC in comparison with the ACT consists of the study JAVELIN Bladder 100 and corresponds to the study pool 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: avelumab + BSC vs. BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
JAVELIN Bladder 100	RCT, open-label, parallel	Adult patients with unresectable, locally advanced or metastatic urothelial carcinoma, who are progression-free[c] after platinum-based first-line chemotherapy[b] and have an ECOG PS ≤ 1	Avelumab + BSC (N = 350) BSC (N = 350)	Screening: ≤ 28 days treatment: until progression[d], withdrawal of consent, unacceptable toxicity, lost to follow-up or end of study observation[e]: outcome-specific, at most until death or end of study	197 centres in Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Korea, Mexico, New Zealand, Netherlands, Norway, Poland, Portugal, Russia, Serbia, Spain, Sweden, Taiwan, United Kingdom, USA 04/2016–ongoing[f] ▪ first data cut-off: 21 October 2019 (primary analysis)[g] ▪ second data cut-off: 19 January 2020 (90-day safety update)	Primary: overall survival secondary: symptoms, health status, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: avelumab + BSC vs. BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

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. 4−6 cycles gemcitabine + cisplatin or gemcitabine + carboplatin.
c. Patients had to have been progression-free for 4-10 weeks according to RECIST criteria version 1.1.
d. At the discretion of the treating investigator and in consultation with the company, treatment with avelumab could be continued even after radiological evidence of progression if the following criteria were met: Absence of clinical signs as well as symptoms of disease progression; no deterioration in ECOG PS; no radiological evidence of rapid progression and no progressive tumours at anatomically critical sites that urgently required an alternative medical intervention.
e. Outcome-specific information is provided in Table 8.
f. The study will continue until the final analysis of overall survival (planned after ≥ 425 deaths in the total population or ≥ 219 deaths in the PD-L1-positive population).
g. Originally planned as an interim analysis and predefined as the time point at which ≥ 315 of all patients randomized as planned (or ≥ 146 in the PD-L1-positive population) have died. By achieving a statistically significant superiority of the intervention arm over the control arm in one of the populations, the primary analysis was then conducted at this time.

AE: adverse event; BSC: best supportive care; ECOG PS: Eastern Cooperative of Oncology Group Performance Status; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: avelumab + BSC vs. BSC

Study	Intervention	Comparison
JAVELIN Bladder 100	Avelumab 10 mg/kg BW IV[a] over about 60 minutes on days 1 and 15 of each 4-week cycle + BSC[b]	BSC[b]
	Dose adjustments were not allowed, treatment interruptions and treatment discontinuation due to toxicity were possible[c]	▪
	Pretreatment 4−6 cycles gemcitabine + cisplatin or gemcitabine + carboplatin **Permitted concomitant treatment** ▪ Surgical interventions and local radiation of isolated lesions for palliative purposes ▪ premedication with antihistamines and paracetamol in the intervention arm was required for the first 4 infusions, thereafter at the physician's discretion **Prohibited prior and concomitant treatment** ▪ Immunotherapeutic agents [d] and immunosuppressants, except for short-term systemic treatment with corticosteroids for the treatment of allergic reactions ▪ systemic anti-cancer therapy, neoadjuvant or adjuvant within ≤ 12 months before randomization and during the study ▪ other biologics or experimental pharmaceuticals except avelumab ▪ additionally in the intervention arm: ▫ treatment with bisphosphonate or denosumab (unless it had been initiated > 14 days before the first avelumab dose) ▫ G-CSF or GM-CSF	

a. According to the SPC, avelumab is to be administered in a dosage of 800 mg IV over 60 minutes once every 2 weeks, irrespective of the BW. According to the EMA assessment, both doses are comparable in terms of efficacy and safety [6,8].
b. At the investigator's discretion; comprises antibiotic treatment, dietary measures, treatment of metabolic disorders, optimum symptom control and pain treatment, but not antitumour therapy.
b. Toxicity-related therapy discontinuations up to treatment discontinuation were possible without relevant deviations from the requirements of the SPC [8].
d. IL-2, IFN-α, antibodies against PD-L1, PD-L2, CD137 or CTLA-4 (including ipilimumab) as well as other antibodies or drugs that stimulate T-cells or are immune checkpoint inhibitors.

BSC: best supportive care; BW: body weight; CD: cluster of differentiation; CTCAE: Common Terminology Criteria for Adverse Events; CTLA: cytotoxic T-lymphocyte-associated antigen; EMA: European Medicines Agency; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IV: intravenous; IFN: interferon; IL: interleukin; PO: orally; PD-L: programmed cell death ligand; RCT: randomized controlled trial

Description of the study

Patient population

The JAVELIN Bladder 100 study is an open-label, randomized, controlled study on the comparison of avelumab + BSC with BSC. The study included adults with unresectable, locally advanced or metastatic stage IV urothelial carcinoma who were progression-free after 4 to 6 cycles of first-line platinum-based chemotherapy according to the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines version 1.1. Patients had to remain progression-free for

at least 4 and a maximum of 10 weeks after completion of the first-line treatment. Another requirement for study inclusion was a general condition according to ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. Patients with brain metastases could be included in the study if treatment of the metastases had been completed and the metastases were stable.

The study included 2 co-primary populations: 1) patients with PD-L1-positive tumours (including infiltrating immune cells; determined by a verified immunohistochemical test) and 2) all randomized patients. A total of 700 patients worldwide were randomized to the intervention arm avelumab + BSC (N = 350) and the control arm BSC (N = 350) in a 1:1 ratio. Randomization was stratified according to the degree of response to platinum-based chemotherapy in first-line treatment (complete or partial response vs. stable disease) and the localization of metastases (visceral vs. non-visceral). As avelumab is approved independent of the PD-L1 status, the total study population was considered for the present benefit assessment.

Interventions

Treatment with avelumab corresponds to the requirements of the SPC without relevant deviations [8]. In the study, avelumab was administered at a dose of 10 mg/kg BW every 2 weeks. According to the SPC, avelumab is to be administered in a dose of 800 mg every 2 weeks, regardless of the body weight [8]. According to the European Medicines Agency (EMA), the two dosing regimens (dependent and independent of body weight) are comparable in terms of efficacy and safety [6]. For the comparison examined in the benefit assessment, it was assumed that the deviation in the dosage of avelumab had no relevant influence on the observed effects.

Patients in both treatment arms received BSC. BSC is administered on an individual basis and according to local practice. Active tumour therapies were excluded, palliative local radiotherapy of isolated lesions was allowed. The therapy in the comparator arm of the study thus corresponds to an adequate implementation of the ACT.

Treatment in both study arms was provided until disease progression, unacceptable toxicity, withdrawal of consent or end of study. In consultation with the sponsor, treatment with avelumab could be continued at the investigator's discretion even after disease progression (even if treatment had been discontinued in the meantime) as long as the patients continue to benefit from the treatment.

Based on the results of the primary analysis, an amendment to the study protocol on 13 February 2020 allowed progression-free patients in the control arm to switch to treatment with avelumab. Since this change was performed after the data cut-offs carried out so far, it had no consequence for the present benefit assessment.

Outcomes

Primary outcome of the JAVELIN Bladder 100 study was overall survival. Patient-relevant secondary outcomes were symptoms, health status and AEs.

Data cut-offs

In the JAVELIN Bladder 100 study, an interim analysis was planned to be performed after 345 patients in the total population had died, when at the same time all patients had been recruited as planned and 146 patients in the PD-L1 positive population had died. In case of a superiority of the intervention arm over the control arm in overall survival in one of the two populations, the interim analysis should at the same time correspond to the primary analysis. The final data cut-off and at the same time the end of the study was planned to take place when 425 and 219 patients in the total population and in the PD-L1-positive population had died, and at the same time the last patient included had been observed for at least 12 months from randomization. Thus, the study was not yet completed at the time of the present benefit assessment. In the dossier, the company presented results on the following data cut-offs:

- First data cut-off of 21 October 2019 (planned interim analysis according to the company; according to the company, the difference in overall survival between the treatment arms at this time already met the criteria to be used as primary analysis)
- Second data cut-off of 19 January 2020 (90-day safety update), subsequently submitted as part of the FDA approval

Due to the prolonged observation, the second data cut-off is irrelevant for the present benefit assessment. As this data cut-off was requested by the FDA, selective reporting is ruled out. However, the company based its conclusions exclusively on the results of the first data cut-off. For the second data cut-off, it only presented updated data on overall survival and on the AEs. For the AEs, it only provided overall rates and without deducting those AEs that represented a progression of the underlying disease. It justified this with the minor change in the number of events between the two data cut-offs, which has no relevant effect on the overall statement of the derivation of the benefit.

Based on the results on the overall rates of the superordinate AE outcomes, it can be estimated that additional events between the first and second data cut-off only occurred in a few patients, and in such a way that the event time analyses of the superordinate outcomes (see Table 28 of the full dossier assessment). In this respect, the analyses of the first data cut-off on the AE outcomes are also considered usable here and are used for the present benefit assessment. Nevertheless, due to the longer observation period it would have been generally desirable for the company to have conducted a complete analysis of all patient-relevant outcomes for the second data cut-off.

Planned duration of follow-up observation

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: avelumab + BSC vs. BSC

Study outcome category outcome	Planned follow-up observation
JAVELIN Bladder 100	
Mortality	
Overall survival	Until withdrawal of consent, lost to follow-up, death, or end of study
Morbidity	
Symptoms (DRS-P and TSE [subscales of the NFBISI-18])	Until 90 days after the last dose of the study medication in the intervention arm or after the last visit in the comparator arm[a]
Health status (EQ-5D VAS)	Until 90 days after the last dose of the study medication in the intervention arm or after the last visit in the comparator arm[a]
Health-related quality of life	Outcome not recorded
Side effects	
All outcomes in the category of side effects	Until 90 days after the last dose of the study medication in the intervention arm or after the last visit in the comparator arm[a,b]

a. The last visit took place in case of disease progression, withdrawal of consent and discontinuation due to toxicity.
b. Follow-up observation of non-serious AEs was terminated when the subsequent therapy was initiated.

AE: adverse event; BSC: best supportive care; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FACT: Functional Assessment of Cancer Therapy; NCCN: National Comprehensive Cancer Network; NFBlSI-18: NCCN/FACT Bladder Symptom Index-18; RCT: randomized controlled trial; TSE: Treatment Side Effects; VAS: visual analogue scale

The outcomes on morbidity and side effects were only observed until 90 days following the termination of treatment, which resulted in systematically shortened observation times. 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.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: avelumab + BSC vs. BSC (multipage table)

Study characteristic category	Avelumab + BSC N = 350	BSC N = 350
JAVELIN Bladder 100		
Age [years], mean (SD)	67 (10)	68 (9)
Sex [F/M], %	24/76	21/79
Region, n (%)		
Europe	214 (61)	203 (58)
North America	12 (3)	22 (6)
Asia	73 (21)	74 (21)
Australasia	34 (10)	37 (11)
Rest of the world	17 (5)	14 (4)
Family origin, n (%)		
Caucasian	232 (66)	238 (68)
Asian	75 (21)	81 (23)
Other	43 (12)	31 (9)
Disease duration: time from first diagnosis to randomization [months]		
Median [min; max]	11.5 [2.4; 178.2]	12.8 [3.3; 448.0]
Mean (SD)	23.9 (29.0)	27.4 (45.0)
ECOG PS at baseline, n (%)		
0	213 (61)	211 (60)
1	136 (39)	136 (39)
2	1 (0)	0 (0)
3	0 (0)	3 (1)
Smoking status at baseline, n (%)		
Never	107 (31)	112 (32)
Current	65 (19)	54 (15)
Former	178 (51)	180 (51)
No data	0 (0)	4 (1)
Localisation of the metastases at the time of initiation of the induction chemotherapy[a], n (%)		
Visceral	191 (55)	191 (55)
Non-visceral	159 (45)	159 (45)
Liver lesions at baseline, n (%)		
Yes	43 (12)	44 (13)
No	307 (88)	306 (87)
Lung lesions at baseline, n (%)		
Yes	83 (24)	83 (24)
No	267 (76)	267 (76)
PD-L1 status at baseline, n (%)		

Table 9: Characteristics of the study population – RCT, direct comparison: avelumab + BSC vs. BSC (multipage table)

Study characteristic category	Avelumab + BSC N = 350	BSC N = 350
Positive	189 (54)	169 (48)
Negative	139 (40)	131 (37)
Unknown	22 (6)	50 (14)
Induction chemotherapy in the first-line setting, n (%)		
Gemcitabine + carboplatin	147 (42)	122 (35)
Gemcitabine + cisplatin	183 (52)	206 (59)
Gemcitabine + carboplatin/cisplatin[b]	20 (6)	20 (6)
missing data	0 (0)	2 (1)
Best response to induction chemotherapy in the first-line setting[a], n (%)		
Complete or partial response	253 (72)	252 (72)
Stable disease	97 (28)	98 (28)
Treatment discontinuation, n (%)	259 (75)	319 (93)
Study discontinuation[c], n (%)	167 (48)	210 (60)

a. According to information in the IRT system on randomization
b. These patients switched between the platinum-containing regimes during their first-line chemotherapy.
c. Among these, 144 deaths were counted in the avelumab + BSC arm and 177 in the BSC arm.

BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IRT: interactive response technology; 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 sufficiently comparable between the two arms of the JAVELIN Bladder 100 study. The average age was 67 and 68 years, and 76% or 79% were male. In both arms, 55% of the patients had visceral metastases. The group of patients with non-visceral metastases also included those with locally advanced urothelial carcinoma. However, the number of these patients in the study and their distribution to the individual arms is not clear from the available documents.

Almost half of the patients had received carboplatin-based chemotherapy in the first-line setting: 42% in the intervention arm and 35% in the comparator arm, 6% each in both arms had received both cisplatin and carboplatin in their first-line therapy. 72% of patients each in both arms had a complete or partial response to platinum-based first-line therapy.

Deviating from the inclusion criteria, a total of 4 patients with ECOG > 1 were included in the study (1 person with ECOG PS 2 in the intervention arm, 3 persons with ECOG PS 3 in the control arm). However, this inclusion was not planned and not systematic, so that it remains unclear whether the observed effects can be transferred to patients with an ECOG PS ≥ 2.

Treatment duration and observation period

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

Table 10: Information on the course of the study – RCT, direct comparison: avelumab + BSC vs. BSC

Study **duration of the study phase** **outcome category**	**Avelumab + BSC** **N = 350**	**BSC** **N = 350**
JAVELIN Bladder 100		
Treatment duration [months][a]		
Median [min; max]	5.7 [0.5; 36.8]	3.0 [0; 35.8]
Mean (SD)	8.9 (7.8)	5.3 (5.7)
Observation period [months]		
Overall survival		
Median [min; max]	13.2 [0.1; 37.4]	10.8 [0.1; 36.4]
Mean (SD)	14.5 (8.3)	12.6 (8.2)
Morbidity		
Symptoms (DRS-P, TSE)		
Median [min; max]	6.3 [0; 36.0]	3.2 [0; 34.9]
Mean (SD)	8.8 (7.5)	5.3 (5.7)
Health status (EQ-5D VAS)		
Median [min; max]	6.4 [0; 36.0]	3.1 [0; 34.9]
Mean (SD)	8.9 (7.6)	5.2 (5.6)
Health-related quality of life	Outcome not recorded[b]	
Side effects[a]		
Median [min; max]	7.9 [0.6; 36.4]	5.7 [0.1; 35.8]
Mean (SD)	10.5 (7.1)	7.6 (5.3)

a. Data based on the safety population: N = 344 (intervention) vs. N = 345 (comparator).
b: Outcome not recorded; the company allocated the NFBISI-18 instrument to health-related quality of life (see Section 2.4.1).

BSC: best supportive care; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FACT: Functional Assessment of Cancer Therapy; max: maximum; min: minimum; N: number of randomized patients; NCCN: National Comprehensive Cancer Network; NFBlSI-18: NCCN/FACT Bladder Symptom Index-18; RCT: randomized controlled trial; SD: standard deviation; TSE: Treatment Side Effects; VAS: visual analogue scale

The median treatment duration in the JAVELIN Bladder 100 study was almost twice as long in the intervention arm as in the comparator arm (5.7 vs. 3.0 months). The outcomes on morbidity and health-related quality of life were collected beyond the end of treatment, however, they were only collected up to a maximum of 90 days after the end of treatment. Therefore, this difference is also reflected in the observation durations for the patient-reported outcomes. However, the differences between the median observation durations for overall survival (13.2

vs. 10.8 months) and AEs (7.9 vs. 5.7 months) are smaller. See Section 2.4.2 for the effects on the outcome-specific risk of bias.

Subsequent therapies

In the JAVELIN Bladder 100 study, there were no restrictions regarding possible 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: avelumab + BSC vs. BSC (JAVELIN Bladder 100)

Study therapy type or drug	Patients with subsequent therapy n (%)	
	avelumab + BSC N = 350	BSC N = 350
JAVELIN Bladder 100		
Total	167 (47.7)	228 (65.1)
Radiotherapy	52 (14.9)	57 (16.3)
Curative	2 (0.6)	3 (0.9)
Palliative	50 (14.3)	54 (15.4)
Surgery	13 (3.7)	14 (4.0)
Drug therapy	148 (42.3)	216 (61.7)
Gemcitabine/gemcitabine hydrochloride	61 (17.4)	52 (14.9)
Paclitaxel	48 (13.7)	41 (11.7)
Carboplatin	46 (13.1)	36 (10.3)
Vinflunine/vinflunine ditartrate	37 (10.6)	17 (4.9)
Cisplatin	29 (8.3)	21 (6.0)
Docetaxel	5 (1.4)	10 (2.9)
Pembrolizumab[a]	19 (5.4)	71 (20.3)
Atezolizumab[a]	3 (0.9)	49 (14.0)
Nivolumab[a]	0 (0)	18 (5.1)
Durvalumab[a]	0 (0)	16 (4.6)
Other[b]	30 (8.6)	39 (11.1)

a. Immune checkpoint inhibitors.
b. All remaining subsequent therapies used in less than ten patients in both study arms, including FGFR inhibitor therapy used in 9 (2.6%) and 8 (2.3%) patients in the intervention and comparator arms, respectively.

BSC: best supportive care; FGFR: fibroblast growth factor receptor; N: number of analysed patients; RCT: randomized controlled trial

The proportion of patients with at least one subsequent therapy was lower in the avelumab + BSC arm than in the BSC arm (47.7% vs. 65.1%). In both treatment arms, the majority of subsequent antineoplastic treatments were drug therapies (42.3% of all patients in the avelumab

+ BSC arm and 61.7% of all patients in the BSC arm). The proportion of therapies with immune checkpoint inhibitors (e.g. pembrolizumab, atezolizumab) was higher in the BSC arm than in the intervention arm. The other subsequent drug therapies showed no clearly uneven distribution between the two arms. About 15% of the patients received radiotherapy in addition to subsequent drug therapies. Most of these radiotherapies were of a palliative nature. In both arms, about 4% of the patients underwent surgery as part of a subsequent therapy.

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: avelumab + BSC vs. BSC

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			
JAVELIN Bladder 100	Yes	Yes	No	No	Yes	Yes	Low
BSC: Best Supportive Care; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the JAVELIN Bladder 100 study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company considers the results of the JAVELIN Bladder 100 study to be transferable to the German health care context. This was derived by the company from data of the Robert Koch Institute (RKI) on patients with bladder carcinoma and from a retrospective study in Germany that included patients with stage IV urothelial carcinoma in various urinary organs and a platinum-based first-line chemotherapy [9,10]. According to the company, the median age of the population in the JAVELIN Bladder 100 study was 68 years, which is within the range of these two data sources (75 years and 66 years). The proportion of men included in the study (77%) is comparable to the gender distribution of bladder cancer in Germany. Moreover, 67% of the study participants were white and 60% came from Europe, which supports the relevance of the results for the German health care context.

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

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 using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy (NFBlSI-18) – DRS-P
  - symptoms, measured using the NFBlSI-18 – TSE instrument
  - health status measured with the EQ-5D VAS
- Health-related quality of life
- Side effects
  - serious AEs (SAEs)
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - infusion-related reactions
  - immune-related 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: avelumab + BSC vs. BSC

Study	Outcomes										
	Overall survival	Symptoms (DRS-P subscale of the NFBISI-18)	Symptoms (TSE-P subscale of the NFBISI-18)[a]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related AEs	Infusion-related reactions	Further specific AEs[b, c]
JAVELIN Bladder 100	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	No[e]	No[e]	No[e]	Yes

a. Without corresponding interaction tests for effect modifiers.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events were considered (coded according to MedDRA version 22.1): hypothyroidism (PT, AEs), gastrointestinal disorders (SOC, SAEs), infections and infestations (SOC, AEs), arthralgia (PT, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), lipase increased (PT, severe AEs), amylase increased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), neoplasms benign, malignant and unspecified (incl cysts and polyps) (including cysts and polyps)" (SOC, severe AEs).
d. Outcome not recorded; the company allocated the NFBISI-18 instrument to health-related quality of life (see text below).
e. No usable data available (see text below).

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FACT: Functional Assessment of Cancer Therapy; MedDRA: Medical Dictionary for Regulatory Activities; NCCN: National Comprehensive Cancer Network; NFBlSI-18: NCCN/FACT Bladder Symptom Index-18; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TSE: Treatment Side Effects; VAS: visual analogue scale

Note on the recording of the outcomes "health-related quality of life" and "symptoms"

The company presented results of the NFBISI-18 to record health-related quality of life. In addition to the NFBlSI-18 total score and the DRS-P subscale, it also presented the subscales TSE, Disease-Related Symptoms - Emotional (DRS-E) and Functional Wellbeing (FWB) as supplementary information, but did not use these to derive an added benefit. Moreover, it analysed the item "the side effects of the treatment bother me" of the TSE subscale under the outcome "morbidity" as part of the patient-reported tolerability. Deviating from the company, the NFBISI-18 was not assigned to health-related quality of life.

The NFBlSI-18 is part of the FACT questionnaire system and asks about the symptoms of patients with bladder cancer [11]. The questionnaire consists of a total of 18 items for men (16 items from the FACT-Bl(adder) and 2 additional items) and 17 items for women, which are

divided into 4 subscales, DRS-P, DRS-E, TSE and FWB. The DRS-P subscale contains 1 item that was only recorded for men. The items are rated by the patients on a 5-point Likert scale from 0 (not at all) to 4 (very much). According to the scoring guidelines, a total score and scores for the individual subscales are to be created. Higher values for the scores mean a lower level of symptoms.

The face validity for the recording of symptoms in patients with bladder cancer was given. However, only the subscales DRS-P and TSE can be clearly assigned to the symptoms. The other 4 items of the DRS-E and FWB subscales are neither suitable to completely represent the complex construct of health-related quality of life, nor can they be specifically assigned to the symptoms. The developers of the NFBlSI-18 also did not assign this to health-related quality of life [12]. According to the scoring guideline, a separate analysis of individual items was not planned [11]. Therefore, the subscales DRS-E and FWB as well as individual analyses of the item "The side effects of the treatment bother me" were not presented.

As no other instruments were used in the JAVELIN Bladder 100 study to assess health-related quality of life, no data on this outcome category were available for the present benefit assessment.

Notes on side effects

Discontinuation due to AEs

In the JAVELIN Bladder 100 study, the AEs that resulted in treatment discontinuation were only recorded in the intervention arm. The company justified this by claiming that BSC could not be discontinued. However, since according to the statistical analysis plan, discontinuations due to AEs should also be explicitly reported in the BSC arm, and since in Module 4 A in the diagram on the patient flow 2 AEs are listed as a reason for treatment discontinuation in the BSC arm, the company's rationale is not entirely comprehensible. Thus, the data situation does not allow for a comparative assessment of the outcome "discontinuation due to AEs" as part of this assessment. The data provided by the company on this outcome are therefore only listed as supplementary information in Table 27 in Appendix B of the full benefit assessment.

Immune-related AEs

In the JAVELIN Bladder 100 study, possible immune-related AEs were initially identified using an a priori defined list of PTs, which the company presents in Module 4 A in Appendix 4-G of the full benefit assessment. However, the recording of immune-related AEs from this list was subject to successive causal linkage. Thus, the AE required treatment with corticosteroids, other immunosuppressants or a hormonal therapy. Next, there had to be no clear alternative explanation for the AE other than the immune-related aetiology and/or there had to be a histopathological or biopsy finding consistent with an immune-related mechanism. This operationalization of causal and thereby stepwise exclusionary linkage is not sufficiently measurable as it does not ensure that all immune-mediated events are captured. The data on immune-related AEs are therefore not usable for the present benefit assessment.

Infusion-related reactions

In the JAVELIN Bladder 100 study, infusion-related reactions were identified using an a priori defined selection of PTs, which the company presented in Module 4 A in Appendix 4-G of the full benefit assessment. However, infusion-related reactions were only recorded in the avelumab + BSC arm. The company stated that no infusion-related reactions were to be expected in the comparator arm, as common BSC measures would not be administered as infusions and a placebo infusion would not be possible due to the open study design. Accordingly, a statement on a comparison between the study arms is not possible. Moreover, in this situation, it is assumed that every event that occurred in the intervention arm was due to the drug, whereby, presumably, the difference between the study arms would have been smaller when compared to a placebo infusion. Therefore, due to the open study design, there are no usable data for the benefit assessment for this outcome.

AEs that represent a progression of the underlying disease

In the JAVELIN Bladder 100 study, progression of the underlying disease detected by imaging techniques should not be documented as an AE. However, symptoms of disease progression were to be recorded as AEs, and as SAEs only in the case of fatal outcome. As a supportive analysis, the company therefore evaluated the overall rates for the superordinate AE outcomes "AEs", "SAEs" and "severe AEs (CTCAE grade ≥ 3)" by excluding events that were due to progression of the underlying disease. For this purpose, the company subsequently excluded the following MedDRA PTs from the analysis: bladder cancer, bladder transitional cell carcinoma, cancer pain, disease progression, malignant neoplasm progression, meningeal metastases, bladder cancer with metastases, neoplasm progression, transitional cell carcinoma, tumour associated fever, tumour bleeding, tumour pain. The approach of the company was adequate. For the present benefit assessment, the analyses of the company were used with the exclusion of events based on the progression of the underlying disease.

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: avelumab + BSC vs. BSC

Study	Study level	Outcomes										
		Overall survival	Symptoms (DRS-P subscale of the NFBISI-18)	Symptoms (TSE-P subscale of the NFBISI-18)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related AEs	Infusion-related reactions	Further specific AEs[a, b]
JAVELIN Bladder 100	L	L	H[c]	H[c]	H[c]	–[d]	H[c]	H[c]	–[e]	–[e]	–[e]	H[c]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events were considered (MedDRA version 22.1): hypothyroidism (PT, AEs), gastrointestinal disorders (SOC, AEs), infections and infestations (SOC, AEs), arthralgia (PT, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), lipase increased (PT, severe AEs), amylase increased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), neoplasms benign, malignant and unspecified (incl cysts and polyps) (including cysts and polyps)" (SOC, severe AEs).
c. Systematically shortened observation time due to complete absence of patients in the analysis and further loss of observations over the course of the study, which differs between the treatment arms and was based on potentially informative reasons. The lack of blinding is important for patient-reported outcomes and the non-severe and non-serious specific AE outcomes.
d. Outcome not recorded; the company allocated the NFBISI-18 instrument to health-related quality of life (see Section 2.4.1).
e. No usable data available; see Section 2.4.1 for reasons.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FACT: Functional Assessment of Cancer Therapy; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NCCN: National Comprehensive Cancer Network; NFBlSI-18: NCCN/FACT Bladder Symptom Index-18; Preferred Term; SAE: serious adverse event; SOC: System Organ Class; TSE: Treatment Side Effects; VAS: visual analogue scale

The risk of bias for the results of the outcome "overall survival" was rated as low. This concurs with the company's assessment.

The risk for bias was rated as high for the patient-reported outcomes of symptoms, measured using the DRS-P and TSE subscales of the NFBlSI-18 questionnaire, and health status, measured with the EQ-5D VAS, . The reason for this is the shortened observation time due to the complete exclusion of patients from the analysis and the further loss of observations over the course of the study. Overall, the loss over the course of the study differed significantly between the treatment arms and, among other things, was largely due to potentially informative reasons. Moreover, the lack of blinding increased the risk of bias in these subjective outcomes.

This deviates from the assessment of the company, which assessed the risk of bias for the results of patient-reported outcomes as low.

The risk of bias for the results of the outcomes "SAEs, "severe AEs" as well as for other specific AEs was rated as high due to incomplete observation for potentially informative reasons. The lack of blinding additionally contributed to the high risk of bias for the results of the non-serious/non-severe AEs. This deviates from the assessment of the company, which, despite the lack of blinding, considers the application of objective and standardized criteria for the recording of AEs as well as the classification according to CTCAE criteria to be sufficient to achieve a low risk for bias.

No usable data are available for the outcomes “discontinuation due to AEs”, “infusion-related reactions” and “immune-related AEs”. Outcomes for the derivation of health-related quality of life were not collected (see Section 2.4.1).

2.4.3 Results

Table 15 and Table 16 summarize the results on the comparison of avelumab + BSC with BSC in adult patients with locally advanced or metastatic urothelial carcinoma in the first-line maintenance treatment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. Kaplan-Meier curves on the used event time analyses can be found in Appendix A of the full dossier assessment. Tables with the common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in Appendix B of the full dossier assessment.

Table 15: Results (mortality, side effects) – RCT, direct comparison: avelumab + BSC vs. BSC (multipage table)

Study outcome category outcome	Avelumab + BSC L	Avelumab + BSC median time to event in months [95% CI] patients with event n (%)	BSC L	BSC median time to event in months [95% CI] patients with event n (%)	avelumab + BSC vs. BSC HR [95% CI]; p-value[a]
JAVELIN Bladder 100					
Mortality					
Overall survival					
First data cut-off (21 October 2019)	350	21.4 [18.9; 26.1] 145 (41.4)	350	14.3 [12.9; 17.9] 179 (51.1)	0.69 [0.56; 0.86]; 0.001
90-Day day safety update (19 January 2020)	350	22.1 [19.0; 26.1] 156 (44.6)	350	14.6 [12.8; 17.8] 190 (54.3)	0.70 [0.56; 0.86]; < 0.001
Side effects, first data cut-off (21 October 2019)					
AEs (supplementary information)[b]	344	0.5 [0.4; 0.5] 338 (98.3)	345	1.3 [1.0; 1.7] 272 (78.8)	–
SAEs[b]	344	28.3 [20.4; NC] 114 (33.1)	345	NA [15.2; NC] 76 (22.0)	1.32 [0.98; 1.76]; 0.066
Severe AEs[b,c]	344	8.8 [6.8; 14.8] 177 (51.5)	345	18.8 [13.4; NC] 101 (29.3)	1.80 [1.41; 2.30]; < 0.001
Discontinuation due to AEs				No usable data[d]	
Specific AEs[c]					
Immune-related AEs				No usable data[d]	
Infusion-related reactions				No usable data[d]	
Hypothyroidism (PT, AEs)	344	NA 40 (11.6)	345	NA 2 (0.6)	19.37 [4.68; 80.21]; < 0.001
Gastrointestinal disorders (SOC, AEs)[e]	344	8.2 [6.7; 10.6] 179 (52.0)	345	24.9 [12.4; NC] 102 (29.6)	1.80 [1.41; 2.30]; < 0.001
Infections and infestations (SOC, AEs)	344	7.4 [5.6; 8.7] 186 (54.1)	345	19.1 [14.0; NC] 105 (30.4)	1.80 [1.41; 2.28]; < 0.001
Arthralgia (PT, AEs)	344	NA 57 (16.6)	345	NA 20 (5.8)	2.59 [1.55; 4.32]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	344	20.2 [14.8; NC] 101 (29.4)	345	NA 36 (10.4)	2.53 [1.72; 3.70]; < 0.001

Table 15: Results (mortality, side effects) – RCT, direct comparison: avelumab + BSC vs. BSC (multipage table)

Study outcome category outcome	Avelumab + BSC		BSC		avelumab + BSC vs. BSC
	L	median time to event in months [95% CI] patients with event n (%)	L	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
Skin and subcutaneous tissue disorders (SOC, AEs)[f]	344	15.1 [9.6; 24.1] 144 (41.9)	345	NA 28 (8.1)	5.94 [3.96; 8.91]; < 0.001
Lipase increased (PT, severe AEs)	344	NA 14 (4.1)	345	NA 1 (0.3)	12.83 [1.68; 97.85]; 0.002
Amylase increased (PT, severe AEs)	344	NA 12 (3.5)	345	NA 2 (0.6)	5.28 [1.17; 23.73]; 0.015
Metabolism and nutrition disorders (SOC, severe AEs)	344	NA 29 (8.4)	345	NA 11 (3.2)	2.24 [1.11; 4.50]; 0.021
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC, severe AEs)	344	NA 9 (2.6)	345	NA [26.0; NC] 17 (4.9)	0.40 [0.18; 0.91]; 0.023

a. Effect and CI: Cox regression; p-value: stratified log-rank test.
b. Under exclusion of events of progression of the underlying disease.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. See Section 2.4.1 of the present benefit assessment.
e. Predominantly the PTs “diarrhoea“, “nausea“ and “vomiting” (see Table 24 of the full dossier assessment).

f. Predominantly the PTs “pruritus“ and “rash” (see Table 24 of the full dossier assessment).

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with at least one event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: avelumab + BSC vs. BSC

Study outcome category outcome	Avelumab + BSC			BSC			avelumab + BSC vs. BSC
	N[a]	values at baseline mean (SD)	change of documentation period mean[b] [95% CI]	N[a]	values at baseline mean (SD)	change of documentation period mean[b] [95% CI]	MD[c] [95% CI]; p-value[d]
JAVELIN Bladder 100							
Morbidity, first data cut-off (21 October 2019)							
Symptoms (DRS-P)	328	27.2 (4.8)	-2.42 [-3.03; -1.82]	319	27.2 (4.8)	-2.89 [-3.60; -2.17]	0.46 [-0.47; 1.40]; 0.329
Symptoms (TSE)	328	15.9 (3.1)	-0.79 [-1.13; -0.46]	319	15.8 (2.9)	-0.90 [-1.30; -0.50]	0.11 [-0.42; 0.63]; 0.688
Health status (EQ-5D VAS)	331	74.9 (18.9)	-5.21 [-7.29; -3.14]	316	74.9 (16.3)	-7.60 [-10.04; -5.16]	2.39 [-0.81; 5.58]; 0.143
Health-related quality of life	Outcome not recorded[e]						

a. Number of patients considered in the analysis for the calculation of the effect estimation, the values at baseline are based on 332 and 329 patients for "health status" and on 335 and 325 patients for "symptoms".
b. Adjusted mean value of change from baseline during the documentation period estimated using MMRM. Positive values correspond to an improvement of symptoms or health status.
c. Adjusted mean difference between the study arms during the documentation period estimated using MMRM.
d. p-value: Wald test.
d. The company allocated the NFBISI-18 instrument to health-related quality of life (see Section 2.4.1).

BSC: best supportive care; CI: confidence interval; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FACT: Functional Assessment of Cancer Therapy; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; NCCN: National Comprehensive Cancer Network; NFBlSI-18: NCCN/FACT Bladder Symptom Index-18; RCT: randomized controlled trial; SD: standard deviation; TSE: Treatment Side Effects; VAS: visual analogue scale

Based on the available data, at most an indication, e.g. of an added benefit, can be derived for the outcome "overall survival", and at most hints for the remaining outcomes due to the high risk of bias. These conclusions all refer to the first data cut-off. The data available on the 90-day safety update suggest no changes with regard to the maximum derivable certainty of conclusions.

Mortality

The first data cut-off (21 October 2019) showed a statistically significant difference between the treatment groups in favour of avelumab + BSC for the outcome "overall survival". The data of the second data cut-off of 19 January 2020 confirmed this result. This resulted in an indication of an added benefit of avelumab + BSC in comparison with BSC.

This concurs with the company's assessment.

Morbidity

The company derived an added benefit with the certainty of conclusion of "indication" across all outcomes on morbidity included by it. Hence, the company's outcome-specific assessment is not described below for these outcomes.

Symptoms (DRS-P)

There was no statistically significant difference between the treatment groups for the outcome "symptoms", recorded using the DRS-P subscale of the NFBISI-18 questionnaire. This resulted in no hint of an added benefit of avelumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Symptoms (TSE)

There was no statistically significant difference between the treatment groups for the outcome "symptoms", recorded using the TSE subscale of the NFBISI-18 questionnaire. This resulted in no hint of an added benefit of avelumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

In the JAVELIN Bladder 100 study, "health status" was recorded with the EQ-5D VAS [13]. The recording is based on a scale from 0 to 100, on which the patients answer the question about their current health status. A score of 0 indicates the worst and a score of 100 the best imaginable health status. The recording of the health status by means of a visual analoge scale (VAS) is regarded as patient-relevant.

There was no statistically significant difference between the treatment groups for the outcome "health status". This resulted in no hint of an added benefit of avelumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

In the JAVELIN Bladder 100 study, no outcome suitable to reflect the health-related quality of life was recorded (for justification, see Section 2.4.1). This resulted in no hint of an added benefit of avelumab + BSC in comparison with BSC; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company used the NFBISI-18 questionnaire to derive an added benefit with regard to health-related quality of life. However, the company also derived no added benefit for this outcome.

Side effects

The company made no statements on greater or lesser harm for individual outcomes. Rather, it does not see any proof of added benefit across all outcomes for the superordinate outcome "side effects". Hence, the company's outcome-specific assessment is not described below for these outcomes.

SAEs

There was no statistically significant difference between the treatment arms for the outcome "SAEs". This resulted in no hint of greater or lesser harm from avelumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference between the treatment groups to the disadvantage of avelumab + BSC was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". As a result, there was a hint of greater harm of avelumab + BSC in comparison with BSC.

Discontinuation due to AEs

No usable data are available for discontinuation due to AEs (see Section 2.4.1 for reasons). This resulted in no hint of greater or lesser harm from avelumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived a statistically significant advantage for avelumab + BSC in comparison with BSC. Therefore, it rated the proportion of discontinuations of 14% in the avelumab + BSC arm as low. Moreover, it used the item "the side effects bother me" from the TSE subscale of the NFBISI-18 questionnaire, which is in favour of avelumab + BSC.

Specific AEs

Immune-related AEs and infusion-related reactions

There are no usable data for each of the outcomes "immune-related AEs" and "infusion-related reactions" (for reasons, see Section 2.4.1). This resulted in no hint of greater or lesser harm from avelumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Hypothyroidism (PT, AEs), gastrointestinal disorders (SOC, AEs), infections and infestations (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs) lipase increased (PT, severe AEs [CTCAE grade ≥ 3]), amylase increased (PT, severe AEs [CTCAE grade ≥ 3]), metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of avelumab + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcomes mentioned. This resulted in a hint of greater harm from avelumab + BSC in comparison with BSC.

Arthralgia (PT, AEs)

A statistically significant difference between the treatment groups to the disadvantage of avelumab + BSC in comparison with BSC was shown for the outcome "arthralgia (PT, AEs)". Moreover, there was an effect modification by the characteristic "age" (see Section 2.4.4). For patients ≥ 65 years of age, there was a hint of greater harm from avelumab + BSC in comparison with BSC. For patients < 65 years of age, there was no hint of greater or lesser harm from

avelumab + BSC in comparison with BSC; greater or lesser harm for patients < 65 years of age is therefore not proven.

Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference between the treatment groups in favour of avelumab + BSC in comparison with BSC was shown for the outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)" (SOC, severe AEs [CTCAE grade ≥ 3])". This resulted in a hint of greater harm from avelumab + BSC in comparison with BSC. However, it is not clear from the information provided by the company in Module 4 of the dossier, which PTs were included in this outcomes. The extent to which events of progression of the underlying disease cause this effect is therefore unclear.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- localisation of the metastases at the time of initiation of the first-line chemotherapy (visceral vs. non-visceral)
- PD-L1 status at baseline (positive versus negative)

All subgroup characteristics used in the present benefit assessment were defined a priori in the JAVELIN Bladder 100 study only for the outcome "overall survival" and for the non-patient-relevant outcomes "progression-free survival", "objective response rate" and "duration of response". There are not subgroup analysis for the outcome "symptoms" - recorded with the TSE subscale of the NFBISI-18 questionnaire.

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. In Module 4 A, the company explained that it was not going to present the interaction p-value if "fewer than ten events had occurred in the subgroups". As the respective event numbers in the individual subgroups are also not stated in Module 4A for the 3 situations in which the company did not present the interaction p-values, it is ultimately impossible to check whether the company's approach is in line with IQWiG methodology [1].

Table 17 shows the results of the subgroup analyses on the comparison of avelumab + BSC with BSC.

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 17: Subgroups (side effects) – RCT, direct comparison: avelumab + BSC vs. BSC

Study outcome characteristic subgroup	Avelumab + BSC L	Avelumab + BSC median time to event in months [95% CI] patients with event n (%)	BSC L	BSC median time to event in months [95% CI] patients with event n (%)	Avelumab + BSC vs. BSC HR [95% CI]	Avelumab + BSC vs. BSC p-value[a]
JAVELIN Bladder 100						
Arthralgia (PT, AEs), first data cut-off (21 October 2019)						
Age						
< 65 years	129	NA 17 (13.2)	106	20.6 [18.8; NC] 10 (9.4)	1.23 [0.56; 2.72]	0.601
≥ 65 years	215	NA 40 (18.6)	239	NA 10 (4.2)	4.01 [2.00; 8.04]	< 0.001
Total					Interaction:	0.024[b]

a. Effect and CI: Cox regression; p-value: log-rank test.
b. p-value: Wald test for the interaction term from a non-stratified Cox regression model with the covariates "treatment", "subgroup characteristic" as well as their interaction "treatment*subgroup characteristic".

BSC: best supportive care; CI: confidence interval; HR: hazard ratio; n: number of patients with at least one event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial

Side effects

Specific AEs

Arthralgia (PT, AEs)

The available subgroup analyses resulted in an effect modification for the outcome "arthralgia (PT, AEs)" by the characteristic "age".

A statistically significant difference between the treatment groups to the disadvantage of avelumab + BSC in comparison with BSC was shown for patients ≥ 65 years". This resulted in a hint of greater harm from avelumab + BSC in comparison with BSC for the subgroup of patients aged ≥ 65 years.

There was no statistically significant difference between the treatment groups for patients < 65 years. This resulted in no hint of greater or lesser harm from avelumab + BSC in comparison with BSC for the subgroup of patients aged < 65 years.

This deviates from the approach of the company in that it presents subgroup analyses but does not take them into account when deriving the added benefit.

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 18).

Determination of the outcome category for the outcomes on side effects

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

Specific AEs

For the specific AEs "hypothyroidism (PT, AEs)", "gastrointestinal disorders (SOC, AEs)", "infections and infestations (SOC, AEs)", "arthralgia (PT, AEs)", "respiratory, thoracic and mediastinal disorders (SOC, AEs)" and "skin and subcutaneous tissue disorders (SOC, AEs)", the majority of the events that occurred in each case were non-serious/non-severe; therefore, these outcomes are assigned to the category "non-serious/non-severe AEs". The company presented no assessment regarding the severity grade of these outcomes.

Table 18: Extent of added benefit at outcome level: avelumab + BSC vs. BSC (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Avelumab + BSC vs. BSC** **median of time to event (months) or mean difference** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival **first data cut-off (21 October 2019)** **90-Day day safety update (19 January 2020)**	 median: 21.4 vs. 14.3 HR: 0.69 [0.56; 0.86]; p = 0.001 median: 22.1 vs. 14.6 HR: 0.70 [0.56; 0.86] p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.95$ added benefit, extent: "considerable"

Table 18: Extent of added benefit at outcome level: avelumab + BSC vs. BSC (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Avelumab + BSC vs. BSC** **median of time to event (months) or mean difference** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Morbidity		
Symptoms (DRS-P)	Mean value in the course of the study: -2.42 vs. -2.89 MD: 0.46 [-0.47; 1.40]; p = 0.329	Lesser benefit/added benefit not proven
Symptoms (TSE)	Mean value in the course of the study: -0.79 vs. -0.90 MD: 0.11 [-0.42; 0.63]; p = 0.688	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean value in the course of the study: -5.21 vs. -7.60 MD: 2.39 [-0.81; 5.58]; p = 0.143	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcome not recorded[c]		
Side effects		
SAEs	Median: 28.3 vs. NA HR: 1.32 [0.98; 1.76]; p = 0.066	Greater/lesser harm not proven
Severe AEs	Median: 8.8 vs. 18.8 HR: 1.80 [1.41; 2.30]; HR: 0.56 [0.43; 0.71][d] p < 0.001 probability: "hint"	Outcome category: severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs	No usable data[e]	Greater/lesser harm not proven
Infusion-related reactions	No usable data[e]	Greater/lesser harm not proven
Immune-related AEs	No usable data[e]	Greater/lesser harm not proven
Hypothyroidism (AEs)	Median: NA vs. NA HR: 19.37 [4.68; 80.21]; HR: 0.05 [0.01; 0.21][d] p < 0.001 probability: "hint"	Outcome category: non serious/ non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Gastrointestinal disorders (AEs)	Median: 8.2 vs. 24.9 HR: 1.80 [1.41; 2.30]; HR: 0.56 [0.43; 0.71][d] p < 0.001 probability: "hint"	Outcome category: non serious/ non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”

Table 18: Extent of added benefit at outcome level: avelumab + BSC vs. BSC (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Avelumab + BSC vs. BSC** **median of time to event (months) or mean difference** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Infections and infestations (AEs)	Median: 7.4 vs. 19.1 HR: 1.80 [1.41; 2.28]; HR: 0.56 [0.44; 0.71][d] p < 0.001 probability: "hint"	Outcome category: non serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Arthralgia (PT) Age < 65 years	Median: NA vs. 20.6 HR: 1.23 [0.56; 2.72]; p = 0.601	Greater/lesser harm not proven
≥ 65 years	Median: NA vs. NA HR: 4.01 [2.00; 8.04]; HR: 0.25 [0.12; 0.50][d] p < 0.001 probability: "hint"	Outcome category: non serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Respiratory, thoracic and mediastinal disorders (AEs)	Median: 20.2 vs. NA HR: 2.53 [1.72; 3.70]; HR: 0.40 [0.27; 0.58][d] p < 0.001 probability: "hint"	Outcome category: non serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Skin and subcutaneous tissue disorders (AEs)	Median: 15.1 vs. NA HR: 5.94 [3.96; 8.91]; HR: 0.17 [0.11; 0.25][d] p < 0.001 probability: "hint"	Outcome category: non serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Lipase increased (severe AE)	Median: NA vs. NA HR: 12.83 [1.68; 97.85]; HR: 0.08 [0.01; 0.60][d] p = 0.002 probability: "hint"	outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% greater harm, extent: “considerable”
Amylase increased (severe AE)	Median: NA vs. NA HR: 5.28 [1.17; 23.73]; HR: 0.19 [0.04; 0.85][d] p = 0.015 probability: "hint"	outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”

Table 18: Extent of added benefit at outcome level: avelumab + BSC vs. BSC (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Avelumab + BSC vs. BSC** **median of time to event (months) or mean difference** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Metabolism and nutrition disorders (severe AE)	Median: NA vs. NA HR: 2.24 [1.11; 4.50]; HR: 0.45 [0.22; 0.90][d] p = 0.021 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (severe AE)	Median: NA vs. NA HR: 0.40 [0.18; 0.91]; p = 0.023 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: “minor”

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. Outcome not recorded; the company allocated the NFBISI-18 instrument to health-related quality of life (see Section 2.4.1).
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. See Section 2.4.1 of the present benefit assessment for reasons.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FACT: Functional Assessment of Cancer Therapy; HR: hazard ratio; MD: mean difference; NA: not achieved; NCCN: National Comprehensive Cancer Network; NFBlSI-18: NCCN/FACT Bladder Symptom Index-18; Preferred Term; SAE: serious adverse event; SMD: standardized mean difference; SOC: System Organ Class; TSE: Treatment Side Effects; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of avelumab in comparison with BSC

Positive effects	**Negative effects**
Mortality ▪ overall survival indication of an added benefit – extent: "considerable"	–
–	Non-serious/non-severe side effects ▪ hypothyroidism, gastrointestinal disorders, infections and infestations, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders in each case: hint of greater harm – extent: "considerable" ▪ arthralgia ▫ Age (≥ 65 years) hint of greater harm – extent: "considerable"
Serious/severe side effects ▪ neoplasms benign, malignant and unspecified (incl cysts and polyps) (severe AE) hint of lesser harm – extent: "minor"	Serious/severe side effects ▪ severe AEs hint of greater harm – extent: "major" including ▫ lipase increased, amylase increased in each case: hint of greater harm – extent: "considerable" ▫ metabolism and nutrition disorders hint of greater harm – extent: "minor"
There are no usable data for “health-related quality of life”, “immune-related reactions”, “infusion-related reactions” and for the outcome “discontinuation due to AEs”. AE: adverse event	

Based on the results presented, probability and extent of the added benefit of the drug avelumab in comparison with the ACT are assessed as follows:

For avelumab + BSC in comparison with BSC, the overall consideration showed both positive and negative effects of different extents and with different probabilities (indication or hint). These relate both to the outcome "overall survival" and to outcomes on side effects of different severity grades

As a positive effect, an indication of a considerable added benefit of avelumab + BSC in comparison with BSC could be determined for the outcome “overall survival”.

For side effects with different severity grades, both positive and negative effects of different extents, each with the probability “hint”, were shown for avelumab + BSC in comparison with BSC. However, these were increasingly to the disadvantage of avelumab + BSC. Greater harm with the extent “major” was found for the outcome “severe AEs”. The remaining effects only occurred in individual specific AEs. For the outcome "neoplasms benign, malignant and

unspecified (incl. cysts and polyps)" in the category "serious/severe AEs" alone, lesser harm with the extent "minor" can be assumed for avelumab + BSC in comparison with BSC. However, it is questionable whether this positive effect is actually to be allocated to the outcome category "side effects" or whether it rather reflects a progression of the disease. Clear demarcation not possible on the basis of the available information.

Since the negative effects do not completely challenge the positive effect for the outcome "overall survival", an indication of a minor added benefit of avelumab + BSC over BSC can be derived for adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free after platinum-based first-line chemotherapy.

Table 20 summarizes the result of the assessment of the added benefit of avelumab in comparison with the ACT.

Table 20: Avelumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy	BSC	Indication of minor added benefit[b]
a. Presentation of the respective ACT specified by the G-BA. b. Almost only patients with an ECOG PS of 0 or 1 were included in the JAVELIN Bladder 100 study. Patients with active brain metastases were excluded. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with active brain metastases. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which, in the overall assessment, derived an indication of major added benefit for adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free after platinum-based chemotherapy.

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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