IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Atezolizumab (urothelial carcinoma after chemotherapy) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Atezolizumab (Urothelkarzinom nach Chemotherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IC	immune cells
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 atezolizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 29 September 2017.

Research question

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

Table 2: Research questions of the benefit assessment of atezolizumab

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

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

One relevant study (IMvigor211) was available for the benefit assessment.

Study pool and patient characteristics

The IMvigor211 study was a randomized, open-label, active-controlled parallel-group study on the comparison of treatment with atezolizumab versus chemotherapy with vinflunine,

paclitaxel or docetaxel. The study included adults with advanced or metastatic urothelial carcinoma who had received at least one prior platinum-containing chemotherapy for advanced or metastatic urothelial carcinoma. These also included patients with progression within 12 months after platinum-based adjuvant/neoadjuvant chemotherapy. The general condition of the patients had to concur with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Hence there were no data for patients with an ECOG PS of ≥ 2.

Overall, 467 patients were randomized to the atezolizumab arm, and 464 patients to the chemotherapy arm of the study. Before randomization, an investigator assigned the chemotherapy (vinflunine, paclitaxel or docetaxel) for the individual patients. For the present assessment, only those patients were relevant for whom treatment with vinflunine was chosen before randomization in case of allocation to the chemotherapy arm. These were 252 patients in the atezolizumab arm and 250 patients in the chemotherapy arm.

Treatment of the patients was in compliance with the specifications of the respective Summaries of Product Characteristics (SPCs). No dose adjustments of atezolizumab were mandated.

Whereas treatment with vinflunine was stopped after progression, continued atezolizumab treatment after progression was allowed for as long as the patient experienced a benefit in the opinion of the investigator. Switching to the treatment of the respective other study arm after progression was not allowed. There were no further restrictions regarding subsequent therapy after progression.

Overall survival was the primary outcome of the study. Secondary patient-relevant outcomes were symptoms, health-related quality of life and adverse events (AEs).

The present assessment was based on the data cut-off from 13 March 2017 prespecified for the analysis on overall survival. No interim analyses were planned. Follow-up observation of the patients is ongoing.

Risk of bias

The risk of bias at study level was rated as low.

The risk of bias for the outcome “overall survival” at outcome level was rated as low.

The risk of bias for the outcomes “symptoms” and “health-related quality of life” was rated as high due to the lack of blinding and potentially informative censoring.

The risk of bias for all outcomes on side effects was rated as high. Depending on the outcome, the reasons include informative censoring, potential selective reporting, differences in treatment and hence observation durations, and lack of blinding.

No usable data or no data at all were available for the outcomes “immune-related AEs” and “serious AEs (SAEs)”.

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

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome “overall survival”. There was no hint of an added benefit of atezolizumab in comparison with vinflunine; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30)

No statistically significant difference was shown between the treatment groups for the symptom outcomes, measured with the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), for each of the scales of **pain, dyspnoea, appetite loss** and **diarrhoea**. This resulted in no hint of an added benefit of atezolizumab for any of these scales; an added benefit is therefore not proven.

There was a statistically significant difference in favour of atezolizumab for each the scales of **fatigue** and **constipation**. Since both outcomes were allocated to the outcome category of non-serious/non-severe symptoms or late complications, the respective extent of the added benefit of atezolizumab was no more than marginal. This resulted in no hint of an added benefit for these outcomes. An added benefit is therefore not proven.

There were statistically significant differences between the treatment groups in favour of atezolizumab for each of the scales of **nausea and vomiting** and **insomnia**. In addition, both scales showed effect modifications by the characteristic “proportion of programmed cell death ligand 1 (PD-L1)-positive immune cells in the tumour biopsy (IC PD-L1)”. For patients with low PD-L1 status (IC0/1), there was a hint of an added benefit of atezolizumab in comparison with vinflunine. For patients with high IC PD-L1 status (IC2/3), there was no hint of an added benefit for atezolizumab; an added benefit is therefore not proven.

Further effect modification by the characteristic “presence of liver metastases at the start of the study” was shown for the scale of **insomnia**. Since this effect modification only occurred in this outcome and there were no data on the investigation of dependencies between the subgroup characteristics “IC PD-L1 status” and “liver metastases” for this outcome, only the effect modification by IC PD-L1 status was used for the assessment of the added benefit for the outcome “insomnia”.

Health-related quality of life

No statistically significant difference was shown for any of the outcomes on health-related quality of life measured with the global health status and the functional scales of the EORTC QLQ-C30. This resulted in no hint of an added benefit of atezolizumab in comparison with vinflunine for any of the functional scales except social functioning; an added benefit is therefore not proven. There was an effect modification by the characteristic "sex" for the outcome "social functioning", however. For men, there was a hint of an added benefit of atezolizumab in comparison with vinflunine. For women, there was no hint of an added benefit; an added benefit is therefore not proven.

Side effects

Severe adverse events (CTCAE grade ≥ 3), serious adverse events, and discontinuation due to adverse events

There were statistically significant differences in favour of atezolizumab for each of the outcomes "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)", "SAEs", and "discontinuation due to AEs". This resulted in a hint of lesser harm of atezolizumab in comparison with vinflunine for each of the 3 outcomes.

Specific adverse events

Immune-related adverse events, serious adverse events and severe adverse events (CTCAE grade ≥ 3)

The dossier contained no usable data or no data at all to allow assessing the added benefit for the outcomes "immune-related AEs" and "immune-related SAEs".

A statistically significant difference to the disadvantage of atezolizumab was shown for the outcome "immune-related severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of greater harm of atezolizumab in comparison with vinflunine for this outcome.

Further specific adverse events

Statistically significant differences in favour of atezolizumab were shown for each of the further outcomes on chosen specific AEs "constipation", "neutropenia" and "febrile neutropenia" (all CTCAE grade ≥ 3). Due to the effect size, which cannot be explained only by confounding factors, the certainty of results on these outcomes was rated as high despite the high risk of bias. This resulted in an indication of lesser harm of atezolizumab in comparison with vinflunine for each of these outcomes.

There were statistically significant differences to the disadvantage of atezolizumab for each of the specific AEs "respiratory, thoracic and mediastinal disorders" and "pneumonitis". This resulted in a hint of greater harm of atezolizumab in comparison with vinflunine for each of these outcomes.

A statistically significant difference in favour of atezolizumab was shown for the specific outcome “mucosal inflammation”. This resulted in a hint of lesser harm of atezolizumab in comparison with vinflunine for this outcome.

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

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

In the overall assessment, there are positive and negative effects of different certainty of results and extent, partly for individual subgroups. On the side of positive effects, there were indications and hints in the outcome categories of non-serious/non-severe side effects and serious/severe side effects and health-related quality of life with the extent “minor” to “major”. These were accompanied by hints of negative effects in therapy-specific serious/severe side effects with the extent “considerable” or “major” or “non-quantifiable”. No hint of lesser benefit or of an added benefit of atezolizumab was shown for overall survival.

In the present assessment, the added benefit was mainly based on a reduction of side effects. The company presented no complete data for the outcomes on side effects for the relevant subpopulation. In addition, the data on immune-related AEs were only usable to a limited extent or were not usable at all.

Overall, there is a hint of considerable added benefit of atezolizumab in comparison with the ACT vinflunine for patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy.

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

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

Table 3: Atezolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy[c]	For patients with early recurrence (≤ 6 months): ▪ **vinflunine** for patients with late recurrence (> 6–12 months): ▪ **vinflunine** or ▪ repeated cisplatin-based chemotherapy[d]	Hint of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the treatment options mentioned above equally apply to patients with progression after platinum-based adjuvant/neoadjuvant chemotherapy.
c: The study underlying the benefit assessment included patients with an ECOG PS of 0 or 1. It is unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
d: For patients who are candidates for this option, depending on course of disease, general condition and tolerability of the first-line treatment.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

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

2.2 Research question

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

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

Table 4: Research questions of the benefit assessment of atezolizumab

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

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on atezolizumab (status: 31 July 2017)
- bibliographical literature search on atezolizumab (last search on 5 July 2017)
- search in trial registries for studies on atezolizumab (last search on 13 July 2017)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 4 October 2017)

The check identified no additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: atezolizumab vs. vinflunine

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
IMvigor211	Yes	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: atezolizumab vs. vinflunine

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
IMvigor211	RCT, open-label, parallel	Adults (≥ 18 years) with locally advanced or metastatic urothelial carcinoma who progressed during or following a platinum-containing chemotherapy, ECOG PS 0 or 1, with a life expectancy of ≥ 12 months	Atezolizumab (N = 467) chemotherapy[b] (N = 464) Relevant analysed subpopulation thereof: atezolizumab (n = 252) vinflunine (n = 250)	▪ Screening: 28 days ▪ Treatment: until progression (or for atezolizumab beyond progression, for as long as the patient experiences a benefit in the opinion of the investigator) or unacceptable toxicity ▪ Follow-up observation: until death, discontinuation of participation in the study, or end of study	198 study centres in Australia, Austria, Belgium, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Japan, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovenia, South Korea, Spain, Sweden, Switzerland, Turkey, United Kingdom, USA 1/2015–ongoing (final data cut-off for overall survival: 13 March 2017)	Primary: overall survival Secondary: symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: Chemotherapy comprised vinflunine or docetaxel or paclitaxel.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: atezolizumab vs. vinflunine

Study	Intervention	Comparison
IMvigor211	Atezolizumab 1200 mg IV every 3 weeks ▪ no dose reduction allowed ▪ dose delay for up to 42 days allowed in case of persistent AEs ▪ dose delay of > 42 days results in treatment discontinuation	Vinflunine IV every 3 weeks at ▪ 320 mg/m² BSA for patients < 75 years with ECOG PS of 0 ▪ 280 mg/m² BSA for patients ≥ 75 to < 80 years with ECOG PS of 1, CrCl ≥ 40 to ≤ 60 mL/min or after radiation of the pelvic area[a] ▪ 250 mg/m² BSA for patients ≥ 80 years with CrCl ≥ 30 to < 40 mL/min
	Pretreatment and concomitant treatment	
	Pretreatment: ▪ at least one platinum-containing chemotherapy for inoperable, advanced or metastatic urothelial carcinoma **Concomitant treatment permitted:** ▪ atezolizumab: premedication only allowed from cycle ≥ 2 ▪ vinflunine: constipation prophylaxis (laxatives, dietary measures) ▪ treatment of infusion-related reactions ▪ corticosteroids for the treatment of AEs ▪ palliative radiotherapy or local treatment (radiotherapy and/or surgery) of no more than 3 lesions **Non-permitted concomitant treatment:** ▪ other antineoplastic treatments ▪ atezolizumab: ▫ traditional herbal drugs, RANKL inhibitors, immunomodulatory or immunosuppressant drugs ▫ G-CSF treatment ▪ vinflunine: CYP3A4 inhibitors and drugs affecting the heart rate	

a: For patients with an ECOG PS of 1 or after radiation of the pelvic area, the dose at the start of the study was 280 mg/m² BSA. If no haematological toxicity resulting in treatment delay or dose reduction occurred during cycle 1, the dose was increased to 320 mg² BSA in the following cycles.

AE: adverse event; BSA: body surface area; CrCl: creatinine clearance; CYP: cytochrome P450; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-CSF: granulocyte colony-stimulating factor; RANKL: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; vs.: versus

The IMvigor211 study was a randomized, open-label, active-controlled parallel-group study on the comparison of treatment with atezolizumab versus chemotherapy with vinflunine, paclitaxel or docetaxel. The study included adults with advanced or metastatic urothelial carcinoma who had received at least one prior platinum-containing chemotherapy for advanced or metastatic urothelial carcinoma. These also included patients with progression within 12 months after platinum-based adjuvant/neoadjuvant chemotherapy. The general condition of the patients had to concur with an ECOG PS of 0 or 1. Hence there were no data for patients with an ECOG PS of ≥ 2.

Overall, 467 patients were randomized to the atezolizumab arm, and 464 patients to the chemotherapy arm of the study. Randomization was stratified by the following factors: type of chemotherapy (vinflunine versus taxanes [paclitaxel or docetaxel]), proportion of PD-L1-possitive immune cells in the tumour biopsy (IC0/1 versus IC2/3), number (0 versus 1/2/3) of risk factors (time since last chemotherapy [< 3 months versus ≥ 3 months], ECOG PS [0 versus ≥ 1], haemoglobin [< 10 mg/dL versus ≥ 10 mg/dL]), and presence of liver metastases (yes versus no). Before randomization, an investigator assigned the chemotherapy (vinflunine, paclitaxel or docetaxel) for the individual patients. The proportion of patients treated with taxanes was limited to 40%. For the present assessment, only those patients were relevant for whom treatment with vinflunine was chosen before randomization in case of allocation to the chemotherapy arm. These were 252 patients in the atezolizumab arm and 250 patients in the chemotherapy arm.

Treatment of the patients was conducted in accordance with the regimen described in Table 7 and was in compliance with the recommendations of the respective SPCs [3,4]. No dose adjustments of atezolizumab were mandated. Discontinuation of the medication for more than 42 days due to persistent AEs resulted in treatment discontinuation.

Whereas treatment with vinflunine was stopped after progression, continued atezolizumab treatment after progression was allowed for as long as the patient experienced a benefit in the opinion of the investigator. Switching to the treatment of the respective other study arm after progression was not allowed. There were no further restrictions regarding subsequent therapy after progression. The company did not present any information on how many patients in the vinflunine population received which subsequent therapy. In relation to the total population, 23% of the patients in the atezolizumab arm and 25% of the patients in the chemotherapy received subsequent therapy. Chemotherapy was the most common subsequent therapy in both arms: 22% in the atezolizumab arm and 20% in the chemotherapy arm. Although switching to treatment of the respective other study arm was not allowed, about 5% of the patients in the atezolizumab received vinflunine, about 5% docetaxel, and about 8% paclitaxel as subsequent therapy. In the chemotherapy arm, 3% of the patients received atezolizumab as subsequent therapy.

Overall survival was the primary outcome of the study. Secondary patient-relevant outcomes were symptoms, health-related quality of life and AEs.

The present assessment was based on the data cut-off from 13 March 2017 prespecified for the analysis on overall survival. No interim analyses were planned. Follow-up observation of the patients is ongoing.

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: atezolizumab vs. vinflunine

Study **Outcome category** **Outcome**	**Planned follow-up**
IMvigor211	
Mortality	
Overall survival	▪ Every 3 months until death, discontinuation of participation in the study, or end of study
Morbidity	
EORTC QLQ-C30 (symptoms[a])	▪ From cycle 2, on the first day (± 3 days) of each cycle (of 21 days) or within 30 days after the last dose of the study medication
Health-related quality of life	
EORTC QLQ-C30[b]	▪ From cycle 2, on the first day (± 3 days) of each cycle (of 21 days) or within 30 days after the last dose of the study medication
Side effects	
All outcomes in the category "side effects"	▪ Up to and including protocol version 4 (21 September 2015), all outcomes on side effects were recorded until 90 days after the last dose. ▪ From protocol version 5 (8 March 2016), AEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs were recorded until 30 days after the last dose of the study medication; SAEs or AEs of special interest until 90 days after the last dose of the study medication.
a: Measured with the of the EORTC QLQ-C30 symptom scales. b: Measured with the EORTC QLQ-C30 functional scales. 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; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus	

The follow-up observation of the patients for the outcome "overall survival" was planned until death, discontinuation of participation in the study or end of study.

The follow-up observation of the patients for the outcomes on symptoms and health-related quality of life was planned until 30 days after the last dose of the study medication.

According to the first 4 versions of the study protocol, all outcomes on side effects had to be recorded until 90 days after the last dose of the study medication. With study protocol version 5, the duration of the follow-up observation was lowered to 30 days for all outcomes on side effects, except SAEs and AEs of special interest (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment for more information).

Hence the observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 or 90 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be

necessary, however, to record these outcomes over the total period of time, as was the case for survival.

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

Table 9: Characteristics of the study populations – RCT, direct comparison: atezolizumab vs. vinflunine

Study **Characteristics** **Category**	**Atezolizumab**	**Vinflunine**
IMvigor211	N[a] = 252	N[a] = 250
Age [years], mean (SD)	66 (10)	66 (9)
Sex [F/M], %	25/75	22/78
ECOG PS, n (%)		
0	112 (44.4)	108 (43.2)
1	140 (55.6)	142 (56.8)
Time since previous chemotherapy < 3 months, n (%)		
Yes	80 (31.7)	80 (32.0)
No	172 (68.3)	170 (68.0)
Ethnicity, n (%)		
Asian	19 (7.5)	22 (8.8)
Black/African American	0 (0)	1 (0.4)
White	196 (77.8)	182 (72.8)
Unknown	37 (14.7)	45 (18.0)
Smoking status, n (%)		
Current smoker	29 (11.5)	36 (14.5)
Ex-smoker	143 (56.7)	142 (57.3)
IC PD-L1 status[b]		
IC2/3	63 (25.0)	65 (26.0)
IC1	110 (43.7)	97 (38.8)
IC0	79 (31.3)	88 (35.2)
Liver metastases, n (%)		
Yes	86 (34.1)	86 (34.4)
No	166 (65.9)	164 (65.6)
Haemoglobin < 10 g/dL, n (%)		
Yes	39 (15.5)	38 (15.2)
No	213 (84.5)	212 (84.8)
Treatment discontinuation, n (%)	213 (84.5)[c]	234 (93.6)[c]
Study discontinuation, n (%)	182 (72.2)[d]	196 (78.4)[d]

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Proportion of PD-L1-positive immune cells in tumour biopsy < 1 % (IC0), ≥ 1 % to < 5 % (IC1), ≥ 5 % to < 10 % (IC2), ≥ 10 % (IC3).
c: Proportion of patients who discontinued treatment due to progression, n (%): atezolizumab arm 180 (71.4) vs. vinflunine 157 (62.8)
d: Proportion of patients for whom death was recorded as the reason for study discontinuation, n (%): atezolizumab arm 177 (70.2) vs. vinflunine arm 184 (73.6).
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IC: immune cells; M: male; n: number of patients in the category; N: number of randomized patients suitable for vinflunine treatment; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were sufficiently balanced between the groups of the IMvigor211 study. The mean age of the patients was 66 years, and about 3 quarters of them were male and white. Slightly more than half of the patients had an ECOG PS of 1, and just under 70% of them had their last chemotherapy ≥ 3 months before. One third of the patients had liver metastases at study inclusion, and about 15% of the patients had a haemoglobin level of under 10 g/dL.

More patients discontinued treatment in the vinflunine arm (94%) than in the atezolizumab arm (85%) of the IMvigor211 study. The main reason for treatment discontinuation in both treatment groups was disease progression. This was the reason for treatment discontinuation for 71% in the atezolizumab arm and for 63% in the vinflunine arm.

The rate of study discontinuations in both treatment groups was above 70%: 72% in the atezolizumab arm and 78% in the vinflunine arm. The main reason for discontinuation of participation in the study was death of the patients. The proportion of patients who died was 70% in the atezolizumab arm and 74% in the vinflunine arm.

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

Table 10: Information on the course of the study – RCT, direct comparison: atezolizumab vs. vinflunine

Study **Duration of the study phase** **Outcome category**	**Atezolizumab**	**Vinflunine**
IMvigor211	N = 247[a]	N = 242[a]
Treatment duration [months]		
Median [min; max]	3.0 [0; 24]	2.1 [0; 23]
Mean (SD)	5.3 (5.7)	3.5 (4.1)
Observation period [months]		
Overall survival		
Median [min; max]	ND[b]	ND[b]
Morbidity, health-related quality of life, side effects[c]	ND	ND

a: Patients who received at least 1 dose of the study medication.
b: Observation period on overall survival in the total population: atezolizumab median [min; max]: 17.3 [0; 24.5] vs. chemotherapy 17.4 [0; 24.4].
c: From protocol version 5 (8 March 2016), AEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs were recorded until 30 days after the last dose of the study medication; SAEs or AEs of special interest until 90 days after the last dose of the study medication.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; vs.: versus

The treatment duration in the vinflunine arm was about 1 third shorter than in the atezolizumab arm. This was caused by the differences in the study and treatment discontinuations in the course of the study.

The dossier contained no information on observation periods of individual outcomes. It can be assumed that the differences in treatment durations in outcomes with time points of observations that are linked to the treatment duration led to differences in observation periods (see Section 2.7.2.4.2 of the full dossier assessment).

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: atezolizumab vs. vinflunine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
IMvigor211	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the IMvigor211 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 included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the EORTC QLQ-C30 symptom scales
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales

- Side effects
  - severe AEs (CTCAE grade ≥ 3)
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 C) (see Section 2.7.2.4.3 of the full dossier assessment).

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

Table 12: Matrix of outcomes – RCT, direct comparison: atezolizumab vs. vinflunine

Study	Outcomes												
	Overall survival	**Symptoms (EORTC QLQ-C30[a])**	**Health-related quality of life (EORTC QLQ-C30[b])**	**Severe AEs (CTCAE grade ≥ 3)**	**SAEs**	**Discontinuation due to AEs**	**Immune-related AEs[c]**	**Immune-related SAEs**	**Immune-related severe AEs (CTCAE grade ≥ 3)**	**Constipation, febrile neutropenia (PT, CTCAE grade ≥ 3**	**Respiratory, thoracic and mediastinal disorders (SOC, SAEs), neutropenia (PT, CTCAE grade ≥ 3)**	**Pneumonitis (PT, SAE)**	**Mucosal inflammation (PT, AE)**
IMvigor211	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	–[e]	Yes	Yes	Yes	Yes	Yes

a: Measured with the of the EORTC QLQ-C30 symptom scales.
b: Measured with the EORTC QLQ-C30 functional scales.
c: Defined as AEs requiring corticosteroids for control and without clear aetiology.
d: No usable data available; for reasons, see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.
e: No data available for the relevant subpopulation

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.4.2 Risk of bias

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

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: atezolizumab vs. vinflunine

Study	Study level	Outcomes												
		Overall survival	Symptoms (EORTC QLQ-C30[a])	Health-related quality of life (EORTC QLQ-C30[b])	Severe AEs (CTCAE grade ≥ 3)	SAEs	Discontinuation due to AEs	Immune-related AEs[c]	Immune-related SAEs	Immune-related severe AEs (CTCAE grade ≥ 3)	Constipation, febrile neutropenia (PT, CTCAE grade ≥ 3	Respiratory, thoracic and mediastinal disorders (SOC, SAEs), neutropenia (PT, CTCAE grade ≥ 3)	Pneumonitis (PT, SAE)	Mucosal inflammation (PT, AE)
IMvigor211	L	L	H[d, e]	H[d, e]	H[e]	H[e,f]	H[d]	–[g]	–[h]	H[f, i]	H[e]	H[i]	H[f, i]	H[d, e]

a: Measured with the of the EORTC QLQ-C30 symptom scales.
b: Measured with the EORTC QLQ-C30 functional scales.
c: Defined as AEs requiring corticosteroids for control and without clear aetiology.
d: Lack of blinding in subjective recording of outcomes.
e: Large proportion of potentially informative censoring.
f: Selective reporting is possible because the results presented (recording until 30 days after treatment discontinuation) deviate from the documentation time planned a priori (until 90 days after treatment discontinuation).
g: No usable data available; for reasons, see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.
h: No data available for the relevant subpopulation.
i: Large difference in median treatment duration (and hence observation period) between the atezolizumab arm (3 months) and the vinflunine arm (2.1 months).

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; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

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

The risk of bias for the outcomes "symptoms" and "health-related quality of life" was rated as high due to the lack of blinding and potentially informative censoring. The company also rated the risk of bias for these outcomes as high, but provided different reasons (see Section 2.7.2.4.2 of the full dossier assessment).

The risk of bias for all outcomes on side effects was rated as high. Depending on the outcome, the reasons include informative censoring, potential selective reporting, differences in treatment and hence observation durations, and lack of blinding (see Section 2.7.2.4.2 of the full dossier assessment).

This assessment concurs with that of the company for the outcome “discontinuation due to AEs”. Deviating from this, the company rated the risk of bias as low for the outcomes “severe AEs (CTCAE grade ≥ 3)” and “SAEs”.

No usable data or no data at all were available for the outcomes “immune-related AEs” and “SAEs” (see Section 2.7.2.4.3 of the full dossier assessment).

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

2.4.3 Results

Table 14 summarizes the results on the comparison of atezolizumab with vinflunine in patients with advanced or metastatic urothelial carcinoma after cisplatin-containing therapy. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations. For binary outcomes with no events occurring in one treatment arm, the effect estimation and the corresponding confidence interval were calculated with a continuity correction of 0.5 in both treatment arms. Kaplan-Meier curves on overall survival can be found in Appendix A of the full dossier assessment. The dossier contained no Kaplan-Meier curves on the remaining outcomes analysed with event time analyses. Results on common AEs are presented in Appendix B of the full dossier assessment.

Table 14: Results – RCT, direct comparison: atezolizumab vs. vinflunine

Study Outcome category Outcome	Atezolizumab N	Atezolizumab Median time to event in months [95 % CI][a] Patients with event n (%)	Vinflunine N	Vinflunine Median time to event in months [95 % CI][a] Patients with event n (%)	Atezolizumab vs. vinflunine HR[b] [95% CI]; p-value[c]
IMvigor211					
Mortality					
Overall survival					
Data cut-off 13 March 2017	252	9.2 [7.9; 10.4] 178 (70.6)	250	8.3 [6.9; 9.6] 184 (73.6)	0.97 [0.78; 1.19]; 0.752
Morbidity					
Symptoms (EORTC QLQ-C30) – time to deterioration[d]					
Fatigue	238	1.4 [0.9; 1.5] 172 (72.3)	230	1.0 [0.8; 1.4] 166 (72.2)	0.80 [0.64; 1.00]; 0.049
Nausea and vomiting	238	5.5 [3.0; 7.6] 111 (46.6)	230	2.8 [2.1; 3.7] 111 (48.3)	0.74 [0.56; 0.97]; 0.031
Pain	238	2.1 [1.5; 2.5] 151 (63.4)	230	1.8 [1.4; 2.4] 132 (57.4)	0.98 [0.76; 1.25]; 0.848
Dyspnoea	237	3.5 [2.8; 5.8] 119 (50.2)	229	3.7 [2.3; 6.0] 102 (44.5)	0.96 [0.73; 1.27]; 0.774
Insomnia	238	3.7 [3.2; 6.4] 115 (48.3)	230	2.8 [2.0; 4.0] 117 (50.9)	0.74 [0.56; 0.96]; 0.026
Decreased appetite	237	2.1 [1.5; 4.2] 132 (55.7)	230	1.9 [1.4; 3.0] 121 (52.6)	0.99 [0.76; 1.28]; 0.924
Constipation	238	4.2 [3.0; 5.6] 113 (47.5)	228	1.9 [1.4; 3.7] 112 (49.1)	0.73 [0.55; 0.96]; 0.023
Diarrhoea	238	6.2 [4.2; 8.4] 98 (41.2)	228	4.9 [3.7; 14.8] 87 (38.2)	0.87 [0.65; 1.18]; 0.375
Health-related quality of life					
Global health status and functional scales (EORTC QLQ-C30) – time to deterioration[d]					
Global health status	236	2.2 [1.5; 2.9] 148 (62.7)	229	1.8 [1.5; 2.3] 130 (56.8)	0.92 [0.71; 1.18]; 0.503
Physical functioning	238	2.1 [1.5; 2.3] 152 (63.9)	230	1.7 [1.4; 2.3] 132 (57.4)	0.95 [0.75; 1.22]; 0.699
Role functioning	238	1.8 [1.4; 2.2] 152 (63.9)	229	1.4 [1.3; 1.6] 146 (63.8)	0.85 [0.67; 1.08]; 0.180
Emotional functioning	238	4.6 [3.1; 7.7] 115 (48.3)	229	4.2 [2.9; 5.8] 98 (42.8)	0.90 [0.68; 1.20], 0.484
Cognitive functioning	238	2.8 [2.2; 3.5] 124 (52.1)	229	2.3 [1.7; 3.1] 118 (51.5)	0.88 [0.68; 1.15]; 0.352
Social functioning	238	2.2 [1.7; 2.8] 143 (60.1)	229	1.4 [1.4; 1.8] 135 (59.0)	0.81 [0.64; 1.04]; 0.100

(continued)

Table 14: Results – RCT, direct comparison: atezolizumab vs. vinflunine (continued)

Study Outcome category Outcome	Atezolizumab N	Atezolizumab Median time to event in months [95 % CI][a] Patients with event n (%)	Vinflunine N	Vinflunine Median time to event in months [95 % CI][a] Patients with event n (%)	Atezolizumab vs. vinflunine HR[b] [95% CI]; p-value[c]
Side effects					
AEs (supplementary information)	247	ND 235 (95.1)	242	ND 238 (98.3)	–
Severe AEs (CTCAE grade ≥ 3)	247	ND 141 (57.1)	242	ND 164 (67.8)	0.57 [0.45; 0.72]; < 0.001[e]
SAEs	247	ND 102 (41.3)	242	ND 130 (53.7)	0.58 [0.45; 0.76]; < 0.001[e]
Discontinuation due to AEs	247	22 (8.9)	242	38 (15.7)	RR: 0.57 [0.35; 0.93]; 0.024[f]
Specific AEs					
Immune-related AEs[g]	No usable data available[h]				
Immune-related SAEs[g]	No data available for the relevant subpopulation[h]				
Immune-related severe AEs[g] (CTCAE grade ≥ 3)	247	14 (5.7)[i]	242	1 (0.4)	RR: 13.72 [1.82; 103.50]; < 0.001[f]
Constipation (CTCAE grade ≥ 3)	247	ND 2 (0.8)	242	ND 21 (8.7)	0.09 [0.02; 0.38]; 0.001[e]
Neutropenia (CTCAE grade ≥ 3)	247	0 (0)	242	38 (15.7)[i]	RR: 0.01 [0.00; 0.21]; < 0.001[f]
Febrile neutropenia (CTCAE grade ≥ 3)	247	ND 1 (0.4)	242	ND 21 (8.7)[i]	0.04 [0.01; 0.32]; 0.002[e]
Respiratory, thoracic and mediastinal disorders (SAE)	247	10 (4.0)	242	1 (0.4)	RR: 9.80 [1.26; 75.95]; 0.007[f]
Pneumonitis (SAE)	247	4 (1.6)	242	0 (0)	RR: –[j] 0.048[f]
Mucosal inflammation	247	ND 12 (4.9)	242	ND 35 (14.5)	0.28 [0.15; 0.55]; < 0.001[e]

(continued)

Table 14: Results – RCT, direct comparison: atezolizumab vs. vinflunine (continued)

a: Calculated with the Brookmeyer-Crowley method.
b: Unless stated otherwise, calculated with Cox model, stratified by PD-L1 status, presence of liver metastases, and number of risk factors.
c: Stratified log-rank test.
d: Time to deterioration of the score by at least 10 points versus the baseline value.
e: Calculated with unstratified Cox model.
f: Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [5]).
g: Defined as AEs requiring corticosteroids for control and without clear aetiology.
h: Operationalization of the overall rates of immune-related AEs unsuitable (see Section 2.7.2.4.3 of the full dossier assessment). Information on immune-related SAEs are missing.
i: Institute's calculation.
j: Effect estimate and 95 % CI not meaningfully interpretable.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; 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; ND: no data; PD-L1: programmed cell death ligand 1, RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival". There was no hint of an added benefit of atezolizumab in comparison with vinflunine; an added benefit is therefore not proven.

This assessment deviates from that of the company, which derived an indication of a non-quantifiable added benefit for overall survival using the data of the total population.

Morbidity

Symptoms (EORTC QLQ-C30)

No statistically significant difference was shown between the treatment groups for the symptom outcomes, measured with the EORTC QLQ-C30 symptom scales, for each of the scales of **pain, dyspnoea, appetite loss** and **diarrhoea**. This resulted in no hint of an added benefit of atezolizumab for any of these scales; an added benefit is therefore not proven.

This concurs with the company's assessment.

There was a statistically significant difference in favour of atezolizumab for each the scales of **fatigue** and **constipation**. Since both outcomes were allocated to the outcome category of non-serious/non-severe symptoms or late complications, the respective extent of the added benefit of atezolizumab was no more than marginal (see Section 2.5.1). This resulted in no hint of an added benefit for these outcomes. An added benefit is therefore not proven.

For the outcome "constipation", this deviates from the assessment of the company, which claimed an indication of an added benefit for this scale.

There were statistically significant differences between the treatment groups in favour of atezolizumab for each of the scales of **nausea and vomiting** and **insomnia**. In addition, both scales showed effect modifications by the characteristic "proportion of PD-L1-positive immune cells in the tumour biopsy (IC PD-L1)". For patients with low PD-L1 status (IC0/1), there was a hint of an added benefit of atezolizumab in comparison with vinflunine (see Table 15). For patients with high IC PD-L1 status (IC2/3), there was no hint of an added benefit for atezolizumab; an added benefit is therefore not proven.

Further effect modification by the characteristic "presence of liver metastases at the start of the study" was shown for the scale of **insomnia**. Since this effect modification only occurred in this outcome and there were no data on the investigation of dependencies between the subgroup characteristics "IC PD-L1 status" and "liver metastases" for this outcome, only the effect modification by IC PD-L1 status was used for the assessment of the added benefit for the outcome "insomnia".

This assessment deviates from that of the company. The company considered no subgroup results for these outcomes and derived an indication of an added benefit for the nausea and vomiting scale. The company derived no added benefit for the insomnia scale.

Health-related quality of life

No statistically significant difference was shown for any of the outcomes on health-related quality of life measured with the global health status and the functional scales of the EORTC QLQ-C30. This resulted in no hint of an added benefit of atezolizumab in comparison with vinflunine for any of the functional scales except social functioning; an added benefit is therefore not proven. There was an effect modification by the characteristic "sex" for the outcome "social functioning", however (see Table 15). For men, there was a hint of an added benefit of atezolizumab in comparison with vinflunine. For women, there was no hint of an added benefit; an added benefit is therefore not proven.

The company considered no subgroup results and derived no added benefit based on its analyses.

Side effects

Severe adverse events (CTCAE grade ≥ 3), serious adverse events, and discontinuation due to adverse events

There were statistically significant differences in favour of atezolizumab for each of the outcomes "severe AEs (CTCAE grade ≥ 3)", "SAEs", and "discontinuation due to AEs". This resulted in a hint of lesser harm of atezolizumab in comparison with vinflunine for each of the 3 outcomes.

This deviates from the assessment of the company, which derived an indication of an added benefit for each of these outcomes.

Specific adverse events

Immune-related adverse events, serious adverse events and severe adverse events (CTCAE grade ≥ 3)

The dossier contained no usable data or no data at all to allow assessing the added benefit for the outcomes "immune-related AEs" and "immune-related SAEs" (see Section 2.7.2.4.3 of the full dossier assessment).

A statistically significant difference to the disadvantage of atezolizumab was shown for the outcome "immune-related severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of greater harm of atezolizumab in comparison with vinflunine for this outcome.

The company only presented descriptive information on immune-related AEs in the dossier and did not use these data for the derivation of an added benefit.

Further specific adverse events

Statistically significant differences in favour of atezolizumab were shown for each of the further outcomes on chosen specific AEs "constipation", "neutropenia" and "febrile neutropenia" (all CTCAE grade ≥ 3). Due to the effect size, which cannot be explained only by confounding factors, the certainty of results on these outcomes was rated as high despite the high risk of bias. This resulted in an indication of lesser harm of atezolizumab in comparison with vinflunine for each of these outcomes.

The company also derived lesser harm for these outcomes, but did not address the probability of the conclusions of the individual outcomes.

There were statistically significant differences to the disadvantage of atezolizumab for each of the specific AEs "respiratory, thoracic and mediastinal disorders" and "pneumonitis". This resulted in a hint of greater harm of atezolizumab in comparison with vinflunine for each of these outcomes.

The company did not consider these outcomes in its analyses.

A statistically significant difference in favour of atezolizumab was shown for the specific outcome "mucosal inflammation". This resulted in a hint of lesser harm of atezolizumab in comparison with vinflunine for this outcome.

The company also derived lesser harm for this outcome, but did not address the probability of the conclusions of this outcome.

2.4.4 Subgroups and other effect modifiers

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

- sex (female versus male)
- age (< 65 years versus ≥ 65 years)
- ethnicity (Caucasian versus Asian versus other)
- IC PD-L1 status (IC0/1 versus IC2/3)
- number of risk factors (0 versus 1/2/3)
- haemoglobin (< 10 g/dL versus ≥ 10 g/dL)
- time since last chemotherapy (< 3 months versus ≥ 3 months)
- liver metastases (yes versus no)

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.

For the outcomes on side effects, only subgroup data on the effect modifiers “sex” and “age” were available for the relevant population.

The subgroup results of atezolizumab in comparison with vinflunine are summarized in Table 15. Where necessary, the data from the dossier were supplemented by the Institute’s calculations.

Table 15: Subgroups (morbidity, health-related quality of life) – direct comparison: atezolizumab vs. vinflunine

Study Outcome Characteristic Subgroup	Atezolizumab N	Atezolizumab Median time to event in months [95% CI] Patients with event n (%)	Vinflunine N	Vinflunine Median time to event in months [95% CI] Patients with event n (%)	Atezolizumab vs. vinflunine HR [95% CI][a]	Atezolizumab vs. vinflunine p-value[b]
IMvigor211						
Symptoms (EORTC QLQ-C30) – time to deterioration[c]						
Nausea and vomiting						
IC PD-L1 status[e]						
IC0/1	177	5.8 [3.5; 8.5] 80 (45.2)	172	2.2 [1.6; 3.4] 89 (51.7)	0.62 [0.46; 0.85]	0.003
IC2/3	61	2.2 [1.4; NC] 31 (50.8)	58	9.9 [2.1; NC] 22 (37.9)	1.43 [0.82; 2.50]	0.207
					Interaction:	0.023[d]
Insomnia						
IC PD-L1 status[e]						
IC0/1	177	4.2 [3.5; 6.7] 83 (46.9)	172	2.1 [1.5; 2.9] 94 (54.7)	0.62 [0.45; 0.84]	0.002
IC2/3	61	3.5 [1.5; 12.6] 32 (52.5)	58	4.4 [3.5; NC] 23 (39.7)	1.41 [0.82; 2.43]	0.213
					Interaction:	0.007[d]
Liver metastases						
Yes	70	2.1 [1.5; 6.2] 34 (48.6)	65	4.0 [1.8; NC] 26 (40.0)	1.23 [0.73; 2.06]	0.444
No	168	4.9 [3.5; 7.9] 81 (48.2)	165	2.8 [1.7; 3.5] 91 (55.2)	0.66 [0.49; 0.90]	0.008
					Interaction:	0.049[d]
Health-related quality of life (EORTC QLQ-C30) – time to deterioration[c]						
Social functioning						
Sex						
Female	59	1.4 [0.9; 2.1] 42 (71.2)	46	1.4 [1.4; 3.4] 30 (65.2)	1.40 [0.86; 2.29]	0.174
Male	179	2.8 [2.1; 5.4] 101 (56.4)	183	1.4 [1.4; 1.9] 105 (57.4)	0.69 [0.52; 0.92]	0.011
					Interaction:	0.022[d]

(continued)

Table 15: Subgroups (morbidity, health-related quality of life) – direct comparison: atezolizumab vs. vinflunine (continued)

a: Calculated with unstratified Cox model.
b: Calculated with unstratified log-rank test.
c: Time to deterioration of the score by at least 10 points versus the baseline value.
d: p-value from likelihood ratio test.
e: Proportion of PD-L1-positive immune cells in tumour biopsy < 1 % (IC0), ≥ 1 % to < 5 % (IC1), ≥ 5 % to < 10 % (IC2), ≥ 10 % (IC3).
CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; IC: immune cells; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Symptoms (EORTC QLQ-C30)

There were effect modifications by the characteristic "IC PD-L1 status" for each of the scales **"nausea and vomiting"** and **"insomnia"**. For both scales, a statistically significant difference in favour of atezolizumab was shown for patients with low IC PD-L1 status (IC0/1). This resulted in a hint of an added benefit of atezolizumab in comparison with vinflunine in each case. Patients with high IC PD-L1 status (IC2/3) showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of atezolizumab; an added benefit is therefore not proven.

Further effect modification by the characteristic "presence of liver metastases at the start of the study" was shown for the scale of **insomnia**. Since this effect modification only occurred in this one outcome and there were no data on the investigation of dependencies between the subgroup characteristics "IC PD-L1 status" and "liver metastases" for this outcome, only the effect modification by IC PD-L1 status was used for the assessment of the added benefit for this outcome.

This assessment deviates from that of the company. The company considered no subgroup results and derived an indication of an added benefit for the total target population for the nausea and vomiting scale. The company derived no added benefit for the insomnia scale.

Health-related quality of life (EORTC QLQ-C30)

An effect modification by the characteristic "sex" for the social functioning scale was shown for the outcome "health-related quality of life" measured with the global health status and the functional scales of the EORTC QLQ-C30. A statistically significant difference in favour of atezolizumab was shown for men. This resulted in a hint of an added benefit of atezolizumab in comparison with vinflunine. For women, there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit for women; an added benefit is therefore not proven.

This assessment deviates from that of the company. The company considered no subgroup results and derived no added benefit based on its analyses.

2.5 Probability and extent of added benefit

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

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in indications or hints of an added benefit or of lesser harm of atezolizumab in comparison with vinflunine, but also in hints of greater harm from atezolizumab than from vinflunine in patients with advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy.

Determination of the outcome category for outcomes on symptoms and side effects

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

It could not be inferred from the dossier that the outcomes on symptoms of the EORTC QLQ-C30 were severe or serious symptoms. These outcomes were therefore assigned to the outcome category “non-serious/non-severe symptoms/late complications”. For the outcomes “nausea and vomiting” and “constipation”, this categorization deviates from the assessment of the company, which rated these outcomes as severe/serious (see Section 2.7.2.4.3 of the full dossier assessment).

The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: atezolizumab vs. vinflunine

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. vinflunine** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	9.2 vs. 8.3 months HR: 0.97 [0.78; 1.19]; p = 0.752	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30) – time to deterioration[c]		
Fatigue	1.4 vs. 1.0 months HR: 0.80 [0.64; 1.00]; p = 0.049	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$[d] Lesser benefit/added benefit not proven
Nausea and vomiting IC PD-L1 status		
IC0/1	5.8 vs. 2.2 months HR: 0.62 [0.46; 0.85]; p = 0.003 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 < CI_u < 0.90$ added benefit, extent "minor"
IC2/3	2.2 vs. 9.9 months HR: 1.43 [0.82; 2.50]; p = 0.207	Lesser benefit/added benefit not proven
Pain	2.1 vs. 1.8 months HR: 0.98 [0.76; 1.25]; p = 0.848	Lesser benefit/added benefit not proven
Dyspnoea	3.5 vs. 3.7 months HR: 0.96 [0.73; 1.27]; p = 0.774	Lesser benefit/added benefit not proven
Insomnia IC PD-L1 status		
IC0/1	4.2 vs. 2.1 months HR: 0.62 [0.45; 0.84]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 < CI_u < 0.90$ added benefit, extent "minor"
IC2/3	3.5 vs. 4.4 months HR: 1.41 [0.82; 2.43]; p = 0.213	Lesser benefit/added benefit not proven
Decreased appetite	2.1 vs. 1.9 months HR: 0.99 [0.76; 1.28]; p = 0.924	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: atezolizumab vs. vinflunine (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. vinflunine** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Constipation	4.2 vs. 1.9 months HR: 0.73 [0.55; 0.96]; p = 0.023	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$[d] Lesser benefit/added benefit not proven
Diarrhoea	6.2 vs. 4.9 months HR: 0.87 [0.65; 1.18]; p = 0.375	Lesser benefit/added benefit not proven
Health-related quality of life		
Global health status and functional scales (EORTC QLQ-C30) – time to deterioration[c]		
Global health status	2.2 vs. 1.8 months HR: 0.92 [0.71; 1.18]; p = 0.503	Lesser benefit/added benefit not proven
Physical functioning	2.1 vs. 1.7 months HR: 0.95 [0.75; 1.22]; p = 0.699	Lesser benefit/added benefit not proven
Role functioning	1.8 vs. 1.4 months HR: 0.85 [0.67; 1.08]; p = 0.180	Lesser benefit/added benefit not proven
Emotional functioning	4.6 vs. 4.2 months HR: 0.90 [0.68; 1.20]; p = 0.484	Lesser benefit/added benefit not proven
Cognitive functioning	2.8 vs. 2.3 months HR: 0.88 [0.68; 1.15]; p = 0.352	Lesser benefit/added benefit not proven
Social functioning		
Sex		
Female	1.4 vs. 1.4 months HR: 1.40 [0.86; 2.29]; p = 0.174	Lesser benefit/added benefit not proven
Male	2.8 vs. 1.4 months HR: 0.69 [0.52; 0.92]; p = 0.011 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent “minor”

(continued)

Table 16: Extent of added benefit at outcome level: atezolizumab vs. vinflunine (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. vinflunine** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Severe AEs (CTCAE grade ≥ 3)	ND vs. ND HR: 0.57 [0.45; 0.72]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ lesser harm, extent: "major"
SAEs	ND vs. ND HR: 0.58 [0.45; 0.76]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Discontinuation due to AEs	8.9 % vs. 15.7 % RR: 0.57 [0.35; 0.93] p = 0.024 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Specific AEs		
Immune-related AEs	No usable data available[f]	
Immune-related SAEs	No data available for the relevant subpopulation[f]	
Immune-related severe AEs (CTCAE grade ≥ 3)	5.7 % vs. 0.4 % RR: 13.72 [1.82; 103.50] RR: 0.07 [0.01; 0.55][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ greater harm, extent: "major"
Constipation (CTCAE grade ≥ 3)	ND vs. ND HR: 0.09 [0.02; 0.38]; p = 0.001 probability: "indication"[g]	Outcome category: serious/severe side effects $CI_u < 0.75$ lesser harm, extent: "major"
Neutropenia (CTCAE grade ≥ 3)	0 % vs. 15.7 % RR: 0.01 [0.00; 0.21] p < 0.001 probability: "indication"[g]	Outcome category: serious/severe side effects $CI_u < 0.75$ lesser harm, extent: "major"
Febrile neutropenia (CTCAE grade ≥ 3)	ND vs. ND HR: 0.04 [0.01; 0.32]; p = 0.002 probability: "indication"[g]	Outcome category: serious/severe side effects $CI_u < 0.75$ lesser harm, extent: "major"
Respiratory, thoracic and mediastinal disorders (SAE)	4 % vs. 0 % RR: 9.80 [1.26; 75.95] RR: 0.10 [0.01; 0.79][e] p = 0.007 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

(continued)

Table 16: Extent of added benefit at outcome level: atezolizumab vs. vinflunine (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Atezolizumab vs. vinflunine** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Pneumonitis (SAE)	1.6 % vs. 0 % RR: – [h]; p = 0.048 probability: “hint”	Outcome category: serious/severe side effects greater harm, extent: “non-quantifiable”
Mucosal inflammation	ND vs. ND HR: 0.28 [0.15; 0.55]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Time to deterioration of the score by at least 10 points versus the baseline value.
d: Greater benefit is not proven because the effect is only marginal.
e: Institute’s calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: Operationalization of the overall rates of immune-related AEs unsuitable (see Section 2.7.2.4.3 of the full dossier assessment). Immune-related SAEs are not shown.
g: The certainty of results is considered high because the observation of such a large effect is not explicable solely by differences in observation periods and potentially informative censorings.
h: Effect estimate and 95 % CI not meaningfully interpretable.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; IC: immune cells; ND: no data; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of atezolizumab in comparison with vinflunine

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ nausea and vomiting (EORTC QLQ-C30) ▫ IC0/1: hint of an added benefit – extent: "minor" ▪ insomnia (EORTC QLQ-C30) ▫ IC0/1: hint of an added benefit – extent: "minor"	
Health-related quality of life ▪ social functioning (EORTC QLQ-C30) ▫ male: hint of an added benefit – extent "minor"	
Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "major" ▪ SAEs: hint of lesser harm – extent: "considerable" ▪ discontinuation due to AEs: hint of lesser harm – extent "minor" ▪ specific AEs: indication of lesser harm – extent: "major" (including constipation, neutropenia, febrile neutropenia [all CTCAE grade ≥ 3] – extent: in each case "major")	Serious/severe side effects ▪ severe AEs: hint of greater harm – extent: "major" (including immune-related AEs [CTCAE grade ≥ 3] – extent: "major"; respiratory, thoracic and mediastinal disorders [SAEs] – extent: "considerable"; pneumonitis [SAE] – extent: "non-quantifiable")
▪ Non-serious/non-severe side effects ▫ specific AE (mucosal inflammation): hint of lesser harm – extent: "considerable"	
No usable results for the relevant subpopulation were available for immune-related AEs and immune-related SAEs.	
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; IC: immune cells; SAE: serious adverse event	

In the overall assessment, there are positive and negative effects of different certainty of results and extent, partly for individual subgroups. On the side of positive effects, there were indications and hints in the outcome categories of non-serious/non-severe side effects and serious/severe side effects and health-related quality of life with the extent "minor" to "major". These were accompanied by hints of negative effects in therapy-specific serious/severe side effects with the extent "considerable" or "major" or "non-quantifiable". No hint of lesser benefit or of an added benefit of atezolizumab was shown for overall survival.

In the present assessment, the added benefit was mainly based on a reduction of side effects. The company presented no complete data for the outcomes on side effects for the relevant subpopulation. In addition, the data on immune-related AEs were only usable to a limited extent or were not usable at all.

Overall, there is a hint of considerable added benefit of atezolizumab in comparison with the ACT vinflunine for patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy.

The result of the assessment of the added benefit of atezolizumab in comparison with the ACT is summarized in Table 18.

Table 18: Atezolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy[c]	For patients with early recurrence (≤ 6 months): ▪ **vinflunine** for patients with late recurrence (> 6–12 months): ▪ **vinflunine** or ▪ repeated cisplatin-based chemotherapy[d]	Hint of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the treatment options mentioned above equally apply to patients with progression after platinum-based adjuvant/neoadjuvant chemotherapy.
c: The study underlying the benefit assessment included patients with an ECOG PS of 0 or 1. It is unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
d: For patients who are candidates for this option, depending on course of disease, general condition and tolerability of the first-line treatment.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of a considerable added benefit of atezolizumab (see Section 2.7.2.8.2 of the full dossier assessment).

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

2.6 List of included studies

Chugai Pharmaceutical. A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy [IMvigor211] [online]. In: JAPIC Clinical Trials Information. [Accessed: 19.10.2017]. URL: http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-142739.

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F. Hoffmann-La Roche. A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy (IMvigor211): study GO29294 ; clinical study report [unpublished]. 2017.

Hoffmann-La Roche. A study of atezolizumab compared with chemotherapy in participants with locally advanced or metastatic urothelial bladder cancer [IMvigor211]: full text view [online]. In: ClinicalTrials.gov. 01.08.2017 [Accessed: 19.10.2017]. URL: https://ClinicalTrials.gov/show/NCT02302807.

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Please see full dossier assessment for full reference list.

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