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Nivolumab (renal cell carcinoma) –

Addendum to Commission A16-24[1]

Addendum

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Abbreviation	Meaning
ACT	appropriate comparator therapy
CSR	clinical study report
EQ-5D	European Quality of Life-5 Dimensions
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MID	minimally important difference
MMRM	mixed-effects model repeated measures
MSKCC	Memorial Sloan Kettering Cancer Center
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

1 Background

On 5 September 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-24 (Nivolumab [renal cell carcinoma] – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments to the dossier assessment [2], the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information, which went beyond the information provided in the dossier on nivolumab [3], to prove the added benefit. To be able to decide on the added benefit, the G-BA therefore requires further analyses. The G-BA's commission comprised the assessment of the sensitivity analyses of the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) with a minimally important difference (MID) of 10 mm submitted by the company as well as the reconsideration of the already conducted assessment of the analyses on the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS) and on the EQ-5D VAS on the basis of the information on the discrepant patient numbers between the dossier and the clinical study report (CSR) subsequently submitted by the company.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

With its comment, the company presented further analyses on health status (recorded with the EQ-5D VAS) for study CA209-025 as well as explanations on the discrepant patient numbers in the analysis of the FKSI-DRS between Module 4 D of the dossier and the CSR [2].

Study CA209-025 was the only relevant study for the benefit assessment of nivolumab in the therapeutic indication of advanced renal cell carcinoma after prior therapy for research question 1 in comparison with the appropriate comparator therapy (ACT) everolimus [1]. In study CA209-025, morbidity (symptoms) was recorded using the instrument FKSI-DRS; health status was recorded using the EQ-5D VAS. The instruments are described in detail in dossier assessment A16-24 [1].

The assessment of the analyses subsequently submitted is presented in the following sections as follows:

- assessment of the analyses on health status subsequently submitted (Section 2.1)
- assessment of the certainty of conclusions of the analyses on the FKSI-DRS already assessed in dossier assessment A16-24 on the basis of the information subsequently submitted on the patients included in the analysis (Section 2.2)

Section 2.3 contains a derivation of the added benefit of nivolumab in comparison with ACT everolimus in the therapeutic indication advanced renal cell carcinoma after prior therapy under consideration of the results of the present addendum and of dossier assessment A16-24.

2.1 Health status

With its original dossier, the company had presented responder analyses for the EQ-5D VAS with the MID of 7 mm defined a priori. The validation study [4] used by the company described an MID of 7 to 10 mm for the EQ-5D VAS, which was determined using an anchor-based approach (7 mm) and a distribution-based approach (10 mm). This approach has a high uncertainty regarding the anchoring; hence an additional sensitivity analysis based on the upper range (10 mm) as MID would have been adequate. This was not available in the dossier. Alternatively, the mixed-effects model repeated measures (MMRM) analysis presented by the company as additional information was used for the benefit assessment.

With its comment, the company subsequently submitted the missing responder analyses on the upper threshold value (MID 10 mm). The analyses were suitable for the benefit assessment and are assessed in the following sections.

The company also presented subgroup analyses on the analysis mentioned above. There were no indications of an effect modification for the characteristics considered in dossier assessment A16-24.

Risk of bias

For the outcome "health status", the results from the analysis of the time to event, as the results from the MMRM analysis before, were considered to have a high risk of bias. This was due to lack of blinding in subjective recording of outcomes, a relevantly high proportion of patients without usable questionnaire at the start of the study, a decreasing return of questionnaires in the course of the study, and potentially informative censoring.

Results

The following Table 1 shows the results on health status, recorded with the EQ-5D VAS instrument.

Table 1: Results on health status – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study Outcome	Nivolumab		Everolimus		Nivolumab vs. everolimus
	N	Median time to event (months) [95% CI] Patients with event n (%)	N	Median time to event (months) [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
CA209-025					
Morbidity – time to deterioration					
Health status (EQ-5D VAS)					
MID 7 mm	406[b]	6.8 [4.9; 11.3] 226 (55.7)	397[b]	3.8 [2.8; 4.7] 237 (59.7)	0.68 [0.57; 0.82] < 0.001
MID 10 mm	406[b]	12.4 [7.0; 16.8] 205 (50.5)	397[b]	4.6 [3.7; 6.3] 222 (55.9)	0.65 [0.54; 0.79] < 0.001

a: HR and 95% CI from Cox model, p-value from log-rank test; each adjusted for values at the start of the study, and additionally possibly also adjusted for MSKCC score (favourable vs. intermediate vs. poor), number of antiangiogenic pretreatments (1 vs. 2), region (USA/Canada vs. Western Europe vs. rest of the world) according to IVRS.

b: At the start of the study, 361 (88.0%) and 344 (83.7%) patients from the nivolumab and everolimus arm were evaluable; patients with missing data were included as "censored".

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IVRS: interactive voice response system; MID: minimally important difference; MSKCC: Memorial Sloan Kettering Cancer Center; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

There was a statistically significant result in favour of nivolumab for the outcome "health status" (EQ-5D VAS) for both MID threshold values. Based on the lower threshold value (7 mm), deterioration under nivolumab occurred after a median time of 6.8 months, and under everolimus already after 3.8 months. This resulted in a hint of an added benefit of nivolumab in comparison with everolimus for the outcome "health status" (EQ-5D VAS).

2.2 Assessment of the certainty of conclusions of the analyses on the FKSI-DRS

Module 4 of the dossier contained inexplicable deviations for the instrument FKSI-DRS regarding the information on "evaluable patients at the respective documentation time" in comparison with the CSR, which were not justified by the company.

With its comment, the company presented an explanation of the deviating information on patient inclusion. The information on the discrepant patient numbers subsequently submitted by the company with the comment was incomplete, however, because it was not presented separately for the treatment groups. Further explanations by the company in the oral hearing [5] were inconsistent with the information provided in the written comments. The company corrected this information after the oral hearing [6]. The information last presented dissolved the discrepancies between the CSR of study CA209-025 and the data presented in Module 4 of the dossier.

Risk of bias and result

For the outcome "symptoms" (FKSI-DRS), the company clarified the deviations in the information on "evaluable patients at the respective documentation time" between Module 4 D and CSR. As explained in the dossier assessment [1], the risk of bias is still rated as high. As a result, there is still a hint of an added benefit of nivolumab in comparison with the ACT. The extent of added benefit can be quantified with the information subsequently submitted (see Section 2.3).

2.3 Extent and probability of added benefit

2.3.1 Derivation of extent and probability of added benefit at outcome level

Hereinafter, the derivation of extent and probability of the added benefit is presented at outcome level under consideration of the present addendum and dossier assessment A16-24. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

Table 2 shows the results of the CA209-025 study relevant for the derivation of the added benefit.

Table 2: Extent of added benefit at outcome level: nivolumab vs. everolimus (research question 1)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab vs. everolimus** **Median time to event or proportion of events or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
MSKCC score		
Favourable/ intermediate	Median: ND vs. ND HR: 0.81 [0.64; 1.02] p = 0.069	Lesser benefit/added benefit not proven
Poor	Median: 15.34 vs. 7.85 months HR: 0.48 [0.32; 0.70] p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
Symptoms (FKSI-DRS)	Median: 4.4 vs. 1.9 months HR: 0.64 [0.54; 0.76] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Health status (EQ-5D VAS)[c]	Median: 6.8 vs. 3.8 months HR: 0.68 [0.57; 0.82] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Health-related quality of life		
	No usable data	Lesser benefit/added benefit not proven
Side effects		
Serious adverse events	Median: 13.44 vs. 12.98 months HR: 0.91 [0.74; 1.12] p = 0.383	Lesser benefit/added benefit not proven

(continued)

Table 2: Extent of added benefit at outcome level: nivolumab vs. everolimus (research question 1) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab vs. everolimus** **Median time to event or proportion of events or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs		
Number of antiangiogenic pretreatments		
1	Median: NA vs. NA HR: 0.64 [0.43; 0.96] p = 0.030 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
2	Median: NA vs. NA HR: 0.34 [0.15; 0.73] p = 0.004 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
Severe AEs (CTCAE grade 3–4)		
Sex		
Male	Median: 8.08 vs. 3.71 months HR: 0.62 [0.50; 0.76] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.90$ added benefit, extent: "considerable"
Female	Median: 4.86 vs. 3.65 months HR: 0.83 [0.59; 1.17] p = 0.291	Outcome category: serious/severe side effects Greater/lesser harm not proven
Specific AEs (infections and infestations)	Qualitative consideration	Outcome category: non-serious/non-severe side effects Greater/lesser harm not proven[d]
Specific AEs (pneumonitis, mucosal inflammation, stomatitis)	Qualitative consideration probability: "hint"	Outcome category: non-serious/non-severe side effects lesser harm, extent: "non-quantifiable", "considerable"[e]
Specific AEs (arthralgia, musculoskeletal pain, myalgia)	Qualitative consideration	Outcome category: non-serious/non-severe side effects Greater harm not excluded[f]
Specific AEs (blood and lymphatic system disorders)	Qualitative consideration probability: "indication"	Outcome category: serious/severe side effects lesser harm, extent: "major"[g]

(continued)

Table 2: Extent of added benefit at outcome level: nivolumab vs. everolimus (research question 1) (continued)

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: In each case results provided for the lower threshold value (MID 7 points); direction of effect for upper threshold value (MID 10 points) consistent in each case.
d: Results on the basis of the rates not statistically significantly different.
e: CI_u of the RR of the rates considered in qualitative terms: pneumonitis $CI_u = 0.60$; mucosal inflammation $CI_u = 0.34$; stomatitis $CI_u = 0.29$. The effect size cannot be determined exactly. With known direction of the bias to the disadvantage of nivolumab, the extent was estimated to be "considerable" ($CI_u < 0.80$).
f: Result on the basis of the rates with known direction of the bias to the disadvantage of nivolumab statistically significant to the disadvantage of nivolumab.
g: CI_u of the RR of the rates considered in qualitative terms: $CI_u = 0.65$. The effect size cannot be determined exactly. With known direction of the bias to the disadvantage of nivolumab, the extent was estimated to be "major" ($CI_u < 0.75$, risk $\geq 5\%$), however.
AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; MSKCC: Memorial Sloan Kettering Cancer Center; NA: not achieved; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The documents subsequently submitted resulted in the following changes in comparison with dossier assessment A16-24:

- There is a hint of considerable added benefit of nivolumab for the outcome "symptoms" (dossier assessment A16-24: hint of a non-quantifiable added benefit).
- There is a hint of minor added benefit of nivolumab for the outcome "health status" (dossier assessment A16-24: hint of a non-quantifiable added benefit).

2.3.2 Overall conclusion on added benefit

Table 3 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of nivolumab in comparison with everolimus (research question 1)

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ MSKCC score poor: indication of an added benefit – extent: “major”	
Morbidity ▪ Symptoms (FKSI-DRS): hint of an added benefit – extent: “considerable” ▪ Health status (EQ-5D VAS): hint of an added benefit – extent: “minor”	
Serious/severe side effects ▪ Discontinuation due to AEs ▫ number of antiangiogenic pretreatments 1: hint of lesser harm – extent: “minor” ▫ number of antiangiogenic pretreatments 2: hint of lesser harm – extent: “major” ▪ Severe AEs (CTCAE grade 3-4) ▫ sex male: hint of lesser harm – extent “considerable” ▪ Specific AE “blood and lymphatic system disorders”: indication of lesser harm – extent: “major”	
Non-serious/non-severe side effects ▪ Specific AEs “pneumonitis”, “mucosal inflammation”, “stomatitis”: hint of lesser harm – extent: “non-quantifiable”, at least “considerable”	Non-serious/non-severe side effects ▪ Specific AEs “arthralgia”, “musculoskeletal pain”, “myalgia”: greater harm not excluded
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MSKCC: Memorial Sloan Kettering Cancer Center; SAE: serious adverse event; VAS: visual analogue scale	

The rating of the extent of added benefit in the 2 outcomes “symptoms” and “health status” did not change the overall result of dossier assessment A16-24:

- There is an indication of a major added benefit of nivolumab in comparison with the ACT everolimus for the subgroup of patients with poor Memorial Sloan Kettering Cancer Center (MSKCC) score.
- There is an indication of considerable added benefit of nivolumab in comparison with the ACT everolimus for the subgroup of patients with favourable/intermediate MSKCC score.

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

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