IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-24

Nivolumab (renal cell 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 *Nivolumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 2016). 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] Due to legal data protection regulations, employees have the right not to be named.

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[3] 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
DMC	data monitoring committee
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)
IVRS	interactive voice response system
MSKCC	Memorial Sloan Kettering Cancer Center
PT	Preferred Term
RANK-L	receptor activator of nuclear factor kappa-B ligand
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nivolumab. 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 2 May 2016.

Research question

The aim of this report was to assess the added benefit of nivolumab as monotherapy in comparison with the appropriate comparator therapy (ACT) in patients with advanced renal cell carcinoma after prior therapy.

From the G-BA's specification of the ACT, the following 2 research questions resulted for the benefit assessment (Table 2):

Table 2: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Adults with advanced renal cell carcinoma after prior therapy	Everolimus
2	Adults with advanced renal cell carcinoma after prior therapy with temsirolimus	Sunitinib
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company concurred with the G-BA's specification on the ACT for both research questions. The company presented no data for research question 2, however.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Result research question 1: adults with advanced renal cell carcinoma after prior therapy

Study pool and study characteristics

The study CA209-025 was included in the benefit assessment. This was a randomized, open-label, active-controlled approval study on the comparison of nivolumab and everolimus.

Adults with advanced or metastatic renal cell carcinoma with at least one but no more than 2 prior antiangiogenic therapies for the advanced disease were included in the study. In addition, patients were allowed to have received pretreatment with no more than 3 systemic

therapies in total; pretreatment with temsirolimus was excluded. The disease must have progressed during or after the last treatment regimen and within 6 months before enrolment. The patients had to be in good general condition (Karnofsky index of ≥ 70%).

Patients were randomly allocated in a ratio of 1:1 to treatment with nivolumab or everolimus. A total of 821 patients were randomized (410 patients to the nivolumab arm and 411 patients to the everolimus arm).

The patients in the nivolumab arm received 3 mg/kg body weight nivolumab intravenously every 2 weeks; dose modification was not allowed. The patients in the everolimus arm received a daily dose of 10 mg everolimus orally; dose modifications were allowed according to the Summary of Product Characteristics (SPC).

Treatment with nivolumab or everolimus could be continued in both study arms also after initial disease progression if there was a clinical benefit and treatment was tolerated. 44.1% (179 of 406 patients) of the patients in the nivolumab arm and 46.1% (183 of 397 patients) of the patients in the everolimus arm continued treatment after initial disease progression. After further disease progression, treatment was to be discontinued.

The planned duration of the CA209-025 study depended on reaching a predefined number of deaths. A planned interim analysis was to be conducted after 398 deaths (70% of the 569 deaths required for the final analysis). The study was stopped prematurely because the formal interim analysis by the Data Monitoring Committee showed a statistically significant advantage of nivolumab for overall survival.

Risk of bias

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

Results

Mortality

A statistically significant advantage of nivolumab was shown for the outcome “overall survival”.

However, there was proof of an effect modification by the characteristic “Memorial Sloan Kettering Cancer Center (MSKCC) score” (favourable versus intermediate versus poor) for this outcome. The results for patients with favourable, intermediate and poor MSKCC score were therefore interpreted separately. A statistically significant difference between the treatment groups was shown for patients with poor MSKCC score; there was an indication of an added benefit of nivolumab in comparison with everolimus for the outcome “overall survival”. For patients with favourable and intermediate MSKCC score, there was no statistically significant difference between nivolumab and everolimus for both characteristics separately or for the category “favourable/intermediate MSKCC score” pooled in a meta-

analysis; hence there was no hint of an added benefit; an added benefit for this patient group is therefore not proven.

Morbidity

A statistically significant result in favour of nivolumab was shown for each of the outcomes "symptoms (recorded with the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]" and "health status (recorded with the European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS])". Under consideration of the respective risk of bias, this resulted in a hint of an added benefit of nivolumab versus everolimus for each of the outcomes "symptoms (FKSI-DRS)" and "health status (EQ-5D VAS)".

Health-related quality of life

There were no usable data for the outcome "health-related quality of life". Hence there was no hint of an added benefit of nivolumab in comparison with everolimus for this outcome; an added benefit is therefore not proven.

Side effects

- Serious adverse events

No statistically significant difference between the treatment arms was shown for the outcome "serious adverse events (SAEs)". Hence there was no hint of an added benefit of nivolumab in comparison with everolimus; an added benefit is therefore not proven.

- Discontinuation due to adverse events

A statistically significant advantage of nivolumab was shown for the outcome "discontinuation due to adverse events (AEs)".

Since there was an indication of an effect modification by the characteristic "number of antiangiogenic pretreatments" (1 versus 2), the results were interpreted separately for patients with one or 2 antiangiogenic pretreatments. For both patient groups, there was a hint of an added benefit of nivolumab in comparison with everolimus for the outcome "discontinuation due to AEs" under consideration of the risk of bias.

- Severe adverse events (CTCAE grade 3-4)

A statistically significant advantage of nivolumab versus everolimus was shown for the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3-4)".

Since there was an indication of effect modification by the characteristic "sex", the results were interpreted separately for men and women. According to the findings, there was a hint of an added benefit of nivolumab in comparison with everolimus for men under consideration of

the risk of bias. For women, there was no hint of an added benefit; an added benefit is therefore not proven for this patient group.

- Specific adverse events

Due to the different observation periods in the 2 treatment arms (bias to the disadvantage of nivolumab) and the missing survival time analyses for these outcomes, only a qualitative interpretation based on rates was conducted. In case of statistically significantly fewer events under nivolumab with a known bias to the disadvantage of nivolumab, lesser harm from nivolumab could be inferred.

Hence there was an indication of lesser harm of nivolumab compared with everolimus for the severe specific AE "blood and lymphatic system disorders". Because of the possible subjective influencing due to the open-label study design, there was a hint of lesser harm for the non-severe specific AEs "pneumonitis", "mucosal inflammation", and "stomatitis".

Greater or lesser harm was not proven for the non-severe AE "infections and infestations". In case of statistically significantly more events under nivolumab with a known bias to the disadvantage of nivolumab, no conclusion could be derived, but greater harm from nivolumab could not be excluded. This was the case for the non-severe specific AEs "arthralgia", "musculoskeletal pain", and "myalgia".

Result research question 2: adults with advanced renal cell carcinoma after prior therapy with temsirolimus

No data were available for the assessment of the added benefit of nivolumab in comparison with sunitinib in patients with advanced renal cell carcinoma after prior therapy with temsirolimus. Hence there was no hint of an added benefit of nivolumab in comparison with the ACT sunitinib. An added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug nivolumab versus the ACT is assessed as follows:

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Research question 1: adults with advanced renal cell carcinoma after prior therapy

Patients with poor MSKCC score

In the overall consideration, there were positive and negative effects for patients with poor MSKCC score. On the positive side, there was an indication of major added benefit of nivolumab for the outcome "overall survival" and hints of a non-quantifiable added benefit for the outcomes "symptoms (FKSI-DRS)" and "health status (EQ-5D VAS)". In addition, there were hints and indications of lesser harm of nivolumab with different extent in the category "side effects". On the negative side, greater harm from nivolumab concerning musculoskeletal pain could not be excluded.

Overall, the mortality advantage of nivolumab was supported by a consistent advantage in morbidity and side effects. The negative effects were so small that they did not raise doubts about the advantages of nivolumab, particularly those regarding overall survival.

In summary, there is an indication of a major added benefit of nivolumab in comparison with the ACT everolimus for the subgroup of patients with poor MSKCC score.

Patients with favourable/intermediate MSKCC score

For patients with favourable/intermediate MSKCC score, an added benefit for overall survival was not proven.

In addition, under consideration of the results that applied to the total population and therefore also to patients with favourable/intermediate MSKCC score, hints and indications of an added benefit or lesser harm of nivolumab with non-quantifiable to major extent remained in the outcome categories "morbidity" and "side effects", however. On the negative side, greater harm from nivolumab concerning musculoskeletal pain could not be excluded. Overall, the extent of added benefit of nivolumab was therefore assessed as considerable.

In summary, 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.

Research question 2: adults with advanced renal cell carcinoma after prior therapy with temsirolimus

Since the company presented no data for the assessment of the added benefit of nivolumab in adults with advanced renal cell carcinoma after prior therapy with temsirolimus, an added benefit of nivolumab is not proven.

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

Table 3: Nivolumab – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Subgroup**	**Extent and probability of added benefit**
Adults with advanced renal cell carcinoma after prior therapy	Everolimus	Favourable/intermediate MSKCC score	Indication of considerable added benefit
		Poor MSKCC score	Indication of major added benefit
Adults with advanced renal cell carcinoma after prior therapy with temsirolimus	Sunitinib	Added benefit not proven	
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MSKCC: Memorial Sloan Kettering Cancer Center			

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

2.2 Research question

The aim of this report was to assess the added benefit of nivolumab as monotherapy in comparison with the ACT in patients with advanced renal cell carcinoma after prior therapy.

From the G-BA's specification of the ACT, the following 4 research questions resulted for the benefit assessment (Table 4):

Table 4: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Adults with advanced renal cell carcinoma after prior therapy	Everolimus
2	Adults with advanced renal cell carcinoma after prior therapy with temsirolimus	Sunitinib
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The patient population of research question 1 (adults with advanced renal cell carcinoma after prior therapy) did not include the patient population of research question 2 (adults with advanced renal cell carcinoma after prior therapy with temsirolimus); these were 2 separate populations.

The company further specified the population of research question 1 (adults with advanced renal cell carcinoma after prior therapy) as patients after prior antiangiogenic therapy. This limitation of the prior therapy had no consequence for the present assessment of the added benefit of nivolumab because it did not result in the exclusion of relevant studies.

The company concurred with the G-BA's specification on the ACT for both research questions. The company presented no data for research question 2, however.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Research question 1: adults with advanced renal cell carcinoma after prior therapy

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on nivolumab (status: 29 March 2016)
- bibliographical literature search on nivolumab (last search on 10 March 2016)
- search in trial registries for studies on nivolumab (last search on 10 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 18 May 2016)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CA209-025	Yes	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of nivolumab in comparison with everolimus consisted of the CA209-025 study and concurred with that of the company.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-025	RCT, open-label, parallel	▪ Adults with advanced or metastatic clear-cell renal cell carcinoma after prior systemic antiangiogenic therapy[b] ▪ Disease progression (during or after the last treatment regimen) within 6 months before study enrolment ▪ Karnofsky index ≥ 70%	Nivolumab (N = 410) everolimus (N = 411)	▪ Screening: within 30 days before randomization ▪ Treatment: until progression[c] or unacceptable toxicity ▪ Observation: outcome-specific, at most until death[d] or discontinuation of study participation	146 study centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Norway, Poland, Romania, Russia, Spain, Sweden, United Kingdom, USA 10/2012–6/2015[e]	Primary: overall survival Secondary: symptoms, health status, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Randomization stratified by region (USA/Canada, Western Europe, rest of the world), MSKCC score at the start of the study (favourable, intermediate, poor), and number of antiangiogenic pretreatments (1, 2).
c: All patients could continue their respective study treatment also after initial progression if there was a clinical benefit and treatment was tolerated. After further disease progression, treatment was to be discontinued.
d: At most 5 years after the primary analysis of survival.
e: Following amendment 15 to the protocol (12 August 2015), the original interim analysis after at least 398 deaths was declared the final analysis (data cut-off: 18 June 2015).
AE: adverse event; N: number of randomized patients; MSKCC: Memorial Sloan Kettering Cancer Center; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study	Intervention	Comparison
CA209-025	Nivolumab 3 mg/kg body weight every 2 weeks IV	Everolimus 10 mg/day orally
	Dose escalation or reduction not allowed	Dose escalation[a] or reduction[b] allowed according to the SPC
	Temporary dose discontinuation of up to 6 weeks[c] was allowed in both study arms	
	Prior therapy ▪ at least 1 but no more than 2 regimens of antiangiogenic therapy for their advanced or metastatic disease, including sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab ▪ treatment with cytokines, vaccines, and cytotoxins ▪ no more than 3 systemic treatments in total for the advanced or metastatic disease ▪ no mTOR inhibitors including everolimus, temsirolimus, sirolimus, ridaforolimus ▪ no cancer treatments or local radiation within 14[d] days before the start of the study medication	
	Concomitant treatment ▪ supportive treatment for disease-related symptoms ▪ palliative radiotherapy (non-target lesions) and palliative surgical resection in case of disease progression ▪ corticosteroids (with minimal systemic uptake, for physiological substitution, for prophylaxis or treatment of non-autoimmune disorders) ▪ hormone replacement therapy if initiated prior to randomization ▪ bisphosphonates and RANK-L inhibitors for treatment of bone metastases if initiated prior to randomization **Restricted concomitant treatment** The following treatments were to be avoided: ▪ live vaccine ▪ strong or moderate CYP3A and/or P-gp inhibitors or strong CYP3A4 activators **Non-permitted concomitant treatment** ▪ immunosuppressants ▪ systemic corticosteroids > 10 mg prednisolone equivalent per day[e] ▪ concurrent antineoplastic treatment	

a: Temporary dose escalations with concurrent use of a strong CYP3A4 activator to 20 mg/day maximum.
b: Dose reduction in case of serious or unacceptable side effects (to 5 mg/day) and concurrent use of a strong CYP3A4 and/or P-gp inhibitor.
c: Temporary dose discontinuation > 6 weeks was allowed for prolonged steroid treatment in case of AEs or if initiated by the medical monitor or study director.
d: No cancer treatment with bevacizumab < 28 days before the start of the study medication.
e: Except for physiological substitution.
AE: adverse event; CYP3A4: cytochrome P450 3A4; IV: intravenous; mTOR: mammalian target of rapamycin; P-gp: P-glycoprotein; RANK-L: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

The CA209-025 study was a randomized, open-label, active-controlled approval study on the comparison of nivolumab and everolimus. It was a multicentre study conducted in 146 study centres in 24 countries.

Adults with advanced or metastatic renal cell carcinoma with at least one but no more than 2 prior antiangiogenic therapies for the advanced disease were included in the study. Prior antiangiogenic therapy was understood to be treatment with drugs including sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab. In addition, patients were allowed to have received pretreatment with no more than 3 systemic therapies in total; pretreatment with temsirolimus was excluded. The disease must have progressed during or after the last treatment regimen and within 6 months before enrolment. The patients had to be in good general condition (Karnofsky index of ≥ 70%).

The population investigated in the study largely corresponded to the therapeutic indication of nivolumab in the present research question. Since no patients were included who had received prior therapy with cytokines alone, no conclusion could be derived from the available data for these patients.

The patients were stratified by region (USA/Canada versus Western Europe versus rest of the world), MSKCC score at the start of the study (information from the interactive voice response system [IVRS]; favourable versus intermediate versus poor) and number of antiangiogenic pretreatments (1 versus 2) and randomly assigned in a ratio of 1:1 to treatment with nivolumab or everolimus. A total of 821 patients were randomized (410 patients to the nivolumab arm and 411 patients to the everolimus arm).

The patients in the nivolumab arm received 3 mg/kg body weight nivolumab intravenously every 2 weeks; dose modification was not allowed. This concurs with the requirement of the SPC [3]. The patients in the everolimus arm received a daily dose of 10 mg everolimus orally; dose modifications were allowed according to the SPC [4].

All patients could receive concomitant palliative radiotherapy of non-target lesions and palliative surgical resection in case of disease progression. Treatment of bone metastases with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors was allowed if this had been initiated before randomization. Immunosuppressant drugs, high-dose systemic corticosteroids and additional antineoplastic treatments were not allowed.

Treatment with nivolumab or everolimus could be continued in both study arms also after initial disease progression if there was a clinical benefit and treatment was tolerated. 44.1% (179 of 406 patients) of the patients in the nivolumab arm and 46.1% (183 of 397 patients) of the patients in the everolimus arm continued treatment after initial disease progression. After further disease progression, treatment was to be discontinued.

Overall survival was the primary outcome of the study; symptoms, health status, health-related quality of life and side effects were secondary outcomes.

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

Table 8: Planned duration of follow-up – RCT, direct comparison: nivolumab vs. everolimus

Study Outcome category Outcome	Planned follow-up
CA209-025	
Mortality	
Overall survival	First follow-up visit[a] and second follow-up visit[b], then every 3 months until death, end of study or withdrawal of consent to be contacted[c]
Morbidity	
Symptoms (FKSI-DRS)	First follow-up visit[a] and second follow-up visit[b, d]
Health status (EQ-5D VAS)	First follow-up visit[a] and second follow-up visit[b], then every 3 months for 1 year, and then every 6 months until death, discontinuation of participation in the study, or lost to follow-up[e]
Side effects	
All outcomes in the category "side effects"	First follow-up visit[a] and second follow-up visit[b] or discontinuation of participation in the study, or lost to follow-up

a: 30 ± 7 days after the last dose of the study medication or on the day of study discontinuation ± 7 days if this was ≥ 37 days after the last dose.
b: 70–84 days after the first follow-up visit (corresponds to 100–121 days after the last dose of the study medication).
c: At most 5 years after the primary analysis of survival.
d: Discrepant information provided in the running text of the study protocol: "The PRO data collection will be […] until death, withdrawal of study consent, or lost to Follow-up".
e: Information from the study protocol; discrepant information in the statistical analysis plan for FKSI-DRS and EQ-5D: planned follow-up only at the first and second follow-up visit.

EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; PRO: patient-reported outcome; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Two follow-up visits after administration of the last dose of the study medication were mandated in the CA209-025 study: one after about 30 days and another one after about 100 days. The outcomes "symptoms", measured with the FKSI-DRS questionnaire and "side effects" were to be recorded until the second follow-up visit. Data for the outcomes "overall survival" and "health status", recorded with the EQ-5D VAS, were to be recorded until death, end of study, or discontinuation of participation in the study.

The planned duration of the CA209-025 study depended on reaching a predefined number of deaths. 569 deaths were required for the final analysis on overall survival. A planned interim analysis was to be conducted after 398 deaths (70% of the events required for the final analysis). The study was ended prematurely because the formal interim analysis conducted by the data monitoring committee (DMC) (data cut-off on 18 June 2015) showed a statistically significant advantage (according to a predefined value of $p < 0.0148$) of nivolumab for overall survival. Subsequently, patients in the everolimus arm were provided with the possibility to participate in an optional extension phase with nivolumab. The present benefit assessment

refers to the results of the data cut-off from 18 June 2015. These data were not affected by the treatment switching.

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

Table 9: Characteristics of the study populations – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study **Characteristics** **Category**	**Nivolumab**	**Everolimus**
CA209-025	N = 410	N = 411
Age [years], mean (SD)	61 (11)	62 (10)
Sex [F/M], %	23/77	26/74
Ethnicity, n (%)		
White	353 (86.1)	367 (89.3)
Black/African American	1 (0.2)	4 (1.0)
Asian	42 (10.2)	32 (7.8)
American Indians/Alaskans	1 (0.2)	0 (0)
Hawaiians/Pacific islanders	0 (0)	1 (0.2)
Other	13 (3.2)	7 (1.7)
Region, n (%)		
USA and Canada	174 (42.4)	172 (41.8)
Western Europe	140 (34.1)	141 (34.3)
Rest of the world	96 (23.4)	98 (23.8)
Disease duration: time between first diagnosis and randomization [years], median [min; max]	2.60 [0.1; 32.7]	2.59 [0.2; 31.0]
MSKCC score at the start of the study (CRF[a]), n (%)		
Favourable	137 (33.4)[b]	145 (35.3)[b]
Intermediate	193 (47.1)[b]	192 (46.7)[b]
Poor	79 (19.3)[b]	74 (18.0)[b]
Unknown	1 (0.2)[b]	0 (0)[b]
Smoker, n (%)		
Current/former	240 (58.5)	207 (50.4)
Never	161 (39.3)	194 (47.2)
Unknown	9 (2.2)	10 (2.4)
Number of antiangiogenic pretreatments, n (%)		
1	317 (77.3)	312 (75.9)
2	90 (22.0)	99 (24.1)
> 2	3 (0.7)	0 (0)
Treatment discontinuation[c], n (%)	339 (82.7[b])	369 (89.8[b])
Study discontinuation, n (%)	189 (46.1[b])	221 (53.8[b])

a: The CSR contained discrepant data on the basis of the CRF or the IVRS.
b: Institute's calculation.
c: Mainly due to disease progression (nivolumab: n = 285; everolimus: n = 273).
CRF: case report form; CSR: clinical study report; F: female; IVRS: interactive voice response system; M: male; max: maximum; min: minimum; MSKCC: Memorial Sloan Kettering Cancer Center; number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and disease-specific patient characteristics were sufficiently comparable between the 2 study arms. The mean age of the patients in the CA209-025 study was 61 and 62 years (nivolumab and everolimus arm). The majority of the patients were male and white and came from the USA, Canada, and Western Europe. The proportion of current or former smokers was 58.5% in the nivolumab arm and 50.4% in the everolimus arm. 39.3% of the patients in the nivolumab arm and 47.2% in the everolimus arm had never smoked.

The median disease duration of the patients at the start of the study was 2.6 months; most patients had a favourable or intermediate MSKCC score. A majority of the patients had received prior antiangiogenic therapy.

The proportion of patients who discontinued treatment was 82.7% in the nivolumab arm and 89.8% in the everolimus arm; treatment discontinuations were largely due to discontinuations due to disease progression. The proportion of patients who discontinued the study was 46.1% and 53.8%; there was no information on reasons.

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

Table 10: Information on the course of the study – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study **Duration of the study phase** **Outcome category**	**Nivolumab**	**Everolimus**
CA209-025	N = 406	N = 397
Treatment duration [months]		
Median [min; max]	5.54 [< 0.1; 29.6]	3.71 [0.2; 25.7]
Mean (SD)	8.85 (7.80)	6.46 (6.40)
Observation period (treatment + follow up observation) [months]		
Overall survival		
Median [min; max]	18.22 [0.3; 30.7]	17.54 [0.5; 31.5]
Mean (SD)	17.03 (7.42)	15.49 (8.12)
Morbidity, side effects		
Median [min; max]	ND	ND
max: maximum; min: minimum; N: number of treated patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus		

The median treatment duration was longer in the nivolumab arm than in the everolimus arm: 5.54 and 3.71 months. The observation period for the outcome “overall survival” was also somewhat longer in the nivolumab arm than in the everolimus arm. No information on follow-up was available for the outcomes of the categories “morbidity” and “side effects”. For the outcomes on symptoms and side effects, a maximum follow-up period of 100 to 121 days after the last dose of the study medication was mandated, however. For these outcomes, the

observation period would therefore differ between the treatment groups. The outcome on health status was also to be recorded until death, study discontinuation, or lost to follow-up, and would therefore presumably not differ to a relevant degree between the treatment groups (see Table 8).

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

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			
CA209-025	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low. This concurs with the company's assessment. Restrictions resulting from the open-label study design and the different observation periods between the treatment arms are described in Section 2.3.2.2 and in Section 2.6.2.4.2 of the full dossier assessment under the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms (FKSI-DRS)
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs

- severe AEs (CTCAE grade 3-4)
- infections and infestations (System Organ Class [SOC])
- pneumonitis (Preferred Term [PT])
- if applicable, further specific AEs (common AEs with potentially important difference between the treatment arms)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 D) (see Section 2.6.2.4.3 of the full dossier assessment).

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

Table 12: Matrix of outcomes – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study	Outcomes							
	Overall survival	symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3-4)	Specific AEs[b]
CA209-025	Yes	Yes	Yes	No[a]	Yes	Yes	Yes	(yes)[c]

a: No usable data available; for reasons, see Section 2.6.2.4.3 of the full dossier assessment.
b: The following events (MedDRA coding) were considered: infections and infestations (SOC), pneumonitis (PT), mucosal inflammation (PT), stomatitis (PT), arthralgia (PT), musculoskeletal pain (PT), myalgia (PT), blood and lymphatic system disorders (SOC, severe AE CTCAE grade 3–4).
d: Results only interpretable in qualitative terms; for reasons, see Sections 2.6.2.4.2 and 2.6.2.4.3 of the full dossier assessment.
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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

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

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study	Study level	Outcomes							
		Overall survival	Symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3-4)	Specific AEs
CA209-025	L	L	H[a]	H[b]	–[c]	H[d]	H[d]	H[d]	H[e]

a: Due to lack of blinding in subjective recording of outcomes, relevantly high proportion of patients without usable questionnaire at the start of the study, decreasing response of questionnaires in the course of the study, and potentially informative censoring.
b: Due to open-label study design with subjective recording of outcomes, relevantly high proportion of patients not considered in the analysis(> 10%) and decreasing response of questionnaires in the course of the study accompanied by potentially informative censoring.
c: No usable data available; for reasons, see Section 2.6.2.4.3 of the full dossier assessment.
d: Due to potentially informative censoring.
e: Due to different median treatment duration (and resulting observation period) in the nivolumab arm (5.5 months) in comparison with the everolimus arm (3.7 months), bias to the disadvantage of nivolumab; in specific AEs rated as serious or severe, the certainty of results was not downgraded in case of a statistically significant effect in favour of nivolumab (see Section 2.6.2.4.2 of the full dossier assessment).

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; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

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

Due to lack of blinding in subjective recording of outcomes, relevantly high proportion of patients without usable questionnaire at the start of the study, decreasing response of questionnaires in the course of the study, and potentially informative censoring, the risk of bias for the outcome “symptoms (FKSI-DRS)” was rated as high. The assessment of a high risk of bias concurs with that of the company.

Due to lack of blinding with subjective recording of outcomes, relevantly high proportion of patients not considered in the analysis(> 10%), and decreasing response of questionnaires in the course of the study accompanied by potentially informative censoring, the risk of bias was also rated as high for the outcome “health status”, recorded with the EQ-5D VAS. The assessment of a high risk of bias concurs with that of the company. However, the company used the EQ-5D VAS data together with the EQ-5D index value for the outcome “health-related quality of life”.

There were no usable data for the outcome “health-related quality of life” (see Section 2.6.2.4.3 of the full dossier assessment for reasons). The risk of bias for this outcome was therefore not assessed. This assessment deviates from that of the company. The company used the data of the EQ-5D and assessed the risk of bias for this outcome as high.

Due to potentially informative censoring, the risk of bias for the outcomes “SAEs”, “discontinuation due to AEs” and “severe AEs (CTCAE grade 3–4)” was rated as high (see Section 2.6.2.4.2 of the full dossier assessment). This assessment partly deviates from that of the company, which rated the risk of bias as high for the outcomes “SAEs” and “discontinuation”, but as low for the outcome “severe AEs (CTCAE grade 3 and 4)”.

Module 4 D contained no analyses for the included outcomes of the specific AEs. The risk of bias for these outcomes was therefore assessed subsequently (see Section 2.6.2.4.2 of the full dossier assessment). Due to the longer treatment duration and the resulting longer observation period in the nivolumab arm (risk of bias to the disadvantage of nivolumab), because of the open-label study design, the certainty of results was downgraded for those outcomes that were rated as non-serious or non-severe and for which a statistically significant result in favour of nivolumab was present.

2.3.2.3 Results

Table 14 and Table 15 summarize the results of the comparison of nivolumab with everolimus in patients with advanced renal cell carcinoma after prior therapy. The Kaplan-Meier curve on overall survival is presented in Appendix A of the full dossier assessment. Specific AEs and common AEs with potentially important difference between the treatment arms are presented in Table 16.

Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

Table 14: Results (survival time) – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study Outcome	Nivolumab		Everolimus		Nivolumab vs. everolimus
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
CA209-025					
Mortality					
Overall survival	410	25.00 [21.75; NA] 183 (44.6)	411	19.55 [17.64; 23.06] 215 (52.3)	0.73 [0.60; 0.89]; 0.002
Morbidity – time to deterioration					
Symptoms (FKSI-DRS)	406[b]	4.4 [3.2; 5.3] 254 (62.6)	397[b]	1.9 [1.9; 2.5] 271 (68.3)	0.64 [0.54; 0.76] < 0.001[c]
Health-related quality of life					
No usable data					
Side effects					
AEs[d] (supplementary information)	406	0.39 [0.26; 0.49] 398 (98.0)	397	0.26 [0.23; 0.33] 385 (97.0)	–
SAEs[d]	406	13.44 [10.09; 17.25] 197 (48.5)	397	12.98 [10.28; 14.82] 188 (47.4)	0.91 [0.74; 1.12]; 0.383
Discontinuation due to AEs[e]	406	NA [26.74; NA] 55 (13.5)	397	NA [24.61; NA] 76 (19.1)	0.51 [0.36; 0.74]; < 0.001
Severe AEs[d, f] (CTCAE grade 3–4)	406	6.93 [6.14; 8.97] 246 (60.6)	397	3.68 [2.79; 4.57] 266 (67.0)	0.64 [0.53; 0.76]; < 0.001

a: HR and 95% CI from Cox model, p-value from log-rank test; each adjusted for MSKCC score (favourable vs. intermediate vs. poor), number of antiangiogenic pretreatments (1 vs. 2), and 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 343 (83.5%) patients from the nivolumab and everolimus arm were evaluable; patients with missing data at the start of the study were included as "censored".
c: Additional adjustment for values at the start of the study.
d: 100-day follow-up without recording of progression of the underlying disease.
e: 30-day follow-up without recording of progression of the underlying disease.
f: Patients whose highest severity grade was a grade 5 AE were considered in this analysis if they had grade 3 or 4 of this AE before.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; IVRS: interactive voice response system; MSKCC: Memorial Sloan Kettering Cancer Center; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 15: Results (continuous outcomes) – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study Outcome category Outcome	Nivolumab			Everolimus			Nivolumab vs. everolimus
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	LS MD [95% CI]; p-value Hedges' g [95% CI]
CA209-025							
Morbidity							
Health status (EQ-5D VAS)	353	73.3 (18.5)	0.6 (0.9)	337	72.3 (18.8)	-5.1 (0.9)	5.7 [3.8; 7.7]; p < 0.001 0.44 [0.28; 0.59]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LSMD: least-square mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Table 16: Results (specific AEs), 100-day follow-up –RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study Outcome category Outcome	Nivolumab		Everolimus	
	N	Patients with event n (%)	N	Patients with event n (%)
CA209-025				
Specific AEs				
Infections and infestations	406	183 (45.1)	397	198 (49.9)
Pneumonitis	406	24 (5.9)	397	61 (15.4)
Common AEs with potentially important difference between the treatment arms				
Mucosal inflammation	406	19 (4.7)	397	87 (21.9)
Stomatitis	406	25 (6.2)	397	126 (31.7)
Arthralgia	406	85 (20.9)	397	59 (14.9)
Musculoskeletal pain	406	42 (10.3)	397	23 (5.8)
Myalgia	406	39 (9.6)	397	16 (4.0)
Blood and lymphatic system disorders (severe AEs with CTCAE grade 3–4)	406	26 (6.4)	397	61 (15.4)

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with at least one event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

At most indications, e.g. of an added benefit, could be derived from the CA209-025 study (see Section 2.3.2.2 and Section 2.6.2.8 of the full dossier assessment).

Mortality

Overall survival

A statistically significant advantage of nivolumab was shown for the outcome "overall survival".

However, there was proof of an effect modification by the characteristic "MSKCC score" (favourable versus intermediate versus poor) for this outcome. The results for patients with favourable, intermediate and poor MSKCC score were therefore interpreted separately (see Section 2.3.2.4). For patients with poor MSKCC score, there was an indication of an added benefit of nivolumab in comparison with everolimus for the outcome "overall survival". For patients with favourable and intermediate MSKCC score, there was no hint of an added benefit for both characteristics separately or for the category "favourable/intermediate MSKCC score" pooled in a meta-analysis; an added benefit for this patient group is therefore not proven.

This deviates from the company's assessment, which interpreted the effect modification by the characteristic "MSKCC score" as a finding that was due to chance. It referred to results of subgroup analyses on further prognostic factors. In some cases patient groups with poor prognosis, and in some cases patients with favourable prognosis showed a statistically significant advantage for these. Hence the company derived an indication of an added benefit of nivolumab for the outcome "overall survival" on the basis of the total population.

Morbidity

Symptoms (FKSI-DRS)

There was a statistically significant result in favour of nivolumab for the outcome "symptoms (FKSI-DRS)". Under consideration of the risk of bias, this resulted in a hint of an added benefit of nivolumab in comparison with everolimus for the outcome "symptoms (FKSI-DRS)".

This assessment deviates from that of the company, which derived an indication of an added benefit of nivolumab for the outcome "symptoms (FKSI-DRS)".

Health status (EQ-5D VAS)

There was a statistically significant result in favour of nivolumab for the outcome "health status (EQ-5D VAS)". Under consideration of the risk of bias, this resulted in a hint of an added benefit of nivolumab in comparison with everolimus for the outcome "health status (EQ-5D VAS)".

This deviates from the company's assessment, which derived an indication of an added benefit of nivolumab for this outcome.

Health-related quality of life

There were no usable data for the outcome "health-related quality of life" (see Section 2.6.2.4.3 of the full dossier assessment). Hence there was no hint of an added benefit of nivolumab in comparison with everolimus for this outcome; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit for the outcome "health-related quality of life" on the basis of the EQ-5D index value.

Side effects

Serious adverse events

No statistically significant difference between the treatment arms was shown for the outcome "SAEs". Hence there was no hint of an added benefit of nivolumab in comparison with everolimus; an added benefit is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to adverse events

A statistically significant advantage of nivolumab was shown for the outcome "discontinuation due to AEs".

Since there was an indication of an effect modification by the characteristic "number of antiangiogenic pretreatments" (1 versus 2), the results were interpreted separately for patients with one or 2 antiangiogenic pretreatments (see Section 2.3.2.4). For both patient groups, there was a hint of an added benefit of nivolumab in comparison with everolimus for the outcome "discontinuation due to AEs" under consideration of the risk of bias.

This assessment deviates from that of the company, which derived the added benefit for the outcome on the basis of the total population. It justified this with effects in the same direction of both subgroups and the total population. Overall, the company derived an indication of an added benefit of nivolumab for the outcome "discontinuation due to AEs".

Severe adverse events (CTCAE grade 3–4)

A statistically significant advantage of nivolumab versus everolimus was shown for the outcome "severe AEs (CTCAE grade 3–4)".

Since there was an indication of effect modification by the characteristic "sex", the results were interpreted separately for men and women (see Section 2.3.2.4). According to the findings, there was a hint of an added benefit of nivolumab in comparison with everolimus for men under consideration of the risk of bias. For women, there was no hint of an added benefit; an added benefit is therefore not proven for this patient group.

This assessment deviates from that of the company, which derived the added benefit for the outcome "severe AEs CTCAE grade 3–4)" on the basis of the total population. It justified this with homogeneous results between the subgroups and the total population. According to the company, the characteristic "female" showed no statistical significance due to the smaller number of patients. Overall, the company derived proof of an added benefit of nivolumab for this outcome.

Specific adverse events

The specific AEs presented in Table 16 were identified while investigating the topic (infections and infestations as well as pneumonitis) and via common AEs with potentially important difference between the treatment arms (mucosal inflammation, stomatitis, arthralgia, musculoskeletal pain, myalgia, and blood and lymphatic system disorders; see Appendix B of the full dossier assessment).

Due to the different observation periods in the 2 treatment arms (bias to the disadvantage of nivolumab) and the missing survival time analyses for these outcomes, only a qualitative interpretation based on rates was conducted. In case of statistically significantly fewer events under nivolumab with a known bias to the disadvantage of nivolumab, lesser harm from nivolumab could be inferred. Hence there was an indication of lesser harm of nivolumab compared with everolimus for the severe specific AE "blood and lymphatic system disorders". Because of the possible subjective influencing due to the open-label study design, there was a hint of lesser harm for the non-severe specific AEs "pneumonitis", "mucosal inflammation", and "stomatitis".

Greater or lesser harm was not proven for the non-severe AE "infections and infestations". In case of statistically significantly more events under nivolumab with a known bias to the disadvantage of nivolumab, no conclusion could be derived, but greater harm from nivolumab could not be excluded. This was the case for the non-severe specific AEs "arthralgia", "musculoskeletal pain", and "myalgia".

2.3.2.4 Subgroups and other effect modifiers

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

- sex (male, female)
- age category I (< 65 years, ≥ 65 years)
- region (USA/Canada, Western Europe, rest of the world)
- MSKCC score (favourable, intermediate, poor)
- number of antiangiogenic pretreatments (1, 2)

All subgroup characteristics and cut-off values mentioned above were predefined in the CA209-025 study for the outcomes “overall survival”, “morbidity”, and “health-related quality of life”. In addition, the characteristics “sex”, “age category” and “region” were described also for the outcomes “SAEs”, “discontinuation due to AEs”, and “severe AEs (CTCAE grade 3–4)” in the statistical analysis plan.

For all subgroup characteristics mentioned, Module 4 D contained usable data on all outcomes included (except for the MMRM analysis of the EQ-5D VAS and specific AEs). The analyses on the outcomes of the category “side effects” referred to the 100-day analyses without recording the progression of the underlying disease. The analyses on the outcome “discontinuation due to AEs”, which referred to the 30-day analyses without recording the progression of the underlying disease, were an exception.

The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$). An indication of differing effects results from a p-value between 0.05 and 0.2.

Hereinafter, results on subgroups with at least an indication of an effect modification and, in addition, a statistically significant and relevant effect in at least one subgroup are presented for the outcomes “overall survival”, “symptoms (FKSI-DRS)”, “SAEs”, “discontinuation due to AEs” and “severe AEs (CTCAE grade 3–4)”.

Table 17: Subgroups (survival time: overall survival) – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median survival time in months [95% CI] Patients with event n (%)	Everolimus N	Everolimus Median survival time in months [95% CI] Patients with event n (%)	Nivolumab vs. everolimus HR [95% CI]	Nivolumab vs. everolimus p-value
CA209-025						
Overall survival						
MSKCC score[a]						
Favourable/intermediate	330[b]	ND 133 (40.3)[b]	337[b]	ND 154 (45.7)[b]	0.81 [0.64; 1.02][c]	0.069[c]
Favourable	137	NA [NA; NA] 38 (27.7)	145	28.98 [26.91; NA] 50 (34.5)	0.80 [0.52; 1.21][d]	0.289[e]
Intermediate	193	21.82 [18.27; NA] 95 (49.2)	192	18.43 [16.13; 23.06] 104 (54.2)	0.81 [0.61; 1.06][d]	0.128[e]
Poor	79	15.34 [9.59; 22.44] 50 (63.3)	74	7.85 [5.42; 9.69] 61 (82.4)	0.48 [0.32; 0.70][d]	< 0.001[e]
Total	410	25.00 [21.75; NA] 183 (44.6)	411	19.55 [17.64; 23.06] 215 (52.3)	Interaction:	0.048[f]

a: Analogous to Module 4 D, patient numbers are based on information provided in the CRF; one patient with unknown MSKCC score was not included in the analysis.
b: Institute's calculation; from information on the subgroups "favourable" and "intermediate" because these subgroups were homogeneous.
c: Institute's calculation; meta-analysis with random effects.
d: From Cox model (no adjustment).
e: Log-rank test (no adjustment).
f: Interaction test across the subgroups "favourable" vs. "intermediate" vs. "poor"; from Cox model with the terms "treatment", "subgroup characteristic", and the interaction term "treatment x subgroup characteristic".
CI: confidence interval; CRF: case report form; HR: hazard ratio; MSKCC: Memorial Sloan Kettering Cancer Center; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 18: Subgroups (survival time: discontinuation due to AEs) – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median survival time in months [95% CI] Patients with event n (%)	Everolimus N	Everolimus Median survival time in months [95% CI] Patients with event n (%)	Nivolumab vs. everolimus HR [95% CI][a]	Nivolumab vs. everolimus p-value
CA209-025						
Discontinuation due to AEs[b]						
Number of antiangiogenic pretreatments						
1	314	NA [26.74; NA] 46 (14.6)	303	NA [24.61; NA] 54 (17.8)	0.64 [0.43; 0.96]	0.030[c]
2	89	NA [25.10; NA] 9 (10.1)	94	NA [16.16; NA] 22 (23.4)	0.34 [0.15; 0.73]	0.004[c]
Total	406	NA [26.74; NA] 55 (13.5)	397	NA [24.61; NA] 76 (19.1)	Interaction	0.139[d]

a: From Cox model (no adjustment).
b: 30-day follow-up period without recording of progression of the underlying disease.
c: Log-rank test (no adjustment).
d: From Cox model with the terms “treatment”, “subgroup characteristic” and the interaction term “treatment x subgroup characteristic”.
AE: adverse event; 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; vs.: versus

Table 19: Subgroups (survival time: severe AEs [CTCAE grade 3–4]) – RCT, direct comparison: nivolumab vs. everolimus (research question 1)

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median survival time in months [95% CI] Patients with event n (%)	Everolimus N	Everolimus Median survival time in months [95% CI] Patients with event n (%)	Nivolumab vs. everolimus HR [95% CI][a]	Nivolumab vs. everolimus p-value
CA209-025						
Severe AEs[b] (CTCAE grade 3–4)						
Sex						
Male	312	8.08 [6.44; 11.99] 181 (58.0)	293	3.71 [2.73; 4.70] 199 (67.9)	0.62 [0.50; 0.76]	< 0.001[c]
Female	94	4.86 [3.98; 7.36] 65 (69.1)	104	3.65 [2.50; 5.55] 67 (64.4)	0.83 [0.59; 1.17]	0.291[c]
Total	406	6.93 [6.14; 8.97] 246 (60.6)	397	3.68 [2.79; 4.57] 266 (67.0)	Interaction	0.120[d]

a: From Cox model (no adjustment).
b: 100-day follow-up without recording of progression of the underlying disease.
c: Log-rank test (no adjustment).
d: From Cox model with the terms "treatment", "subgroup characteristic" and the interaction term "treatment x subgroup characteristic".
AE: adverse event; 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; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

There was proof of an effect modification by the characteristic "MSKCC score" for the outcome "overall survival". A significant effect in favour of nivolumab was shown for patients with poor MSKCC score. For patients with poor MSKCC score, this resulted in an indication of an added benefit of nivolumab in comparison with everolimus for the outcome "overall survival". No statistically significant difference between the treatment arms was shown in both separate subgroups with favourable and intermediate MSKCC score or in the subgroup "favourable/intermediate MSKCC score" pooled in a meta-analysis. For patients with favourable/intermediate MSKCC score, there was therefore no hint of an added benefit of nivolumab in comparison with everolimus; an added benefit for this subgroup is therefore not proven.

This deviates from the assessment of the company, which identified the proof for the effect modification by the characteristic "MSKCC score", but considered it against the background

of the results on subgroup analyses on further prognostic factors (Heng criteria, time from diagnosis to the start of the first systemic treatment). According to the company, in some cases these showed an advantage for the subgroups with favourable prognosis, and in some cases an advantage for those with poor prognosis, so that the observed effects were to be assessed as findings due to chance. In contrast to the MSKCC score, these further prognostic factors investigated by the company only produced a narrow indication of an effect modification. Besides, in contrast to the MSKCC score, these were not stratification factors, so that there was an uncertainty regarding the similarity of the subgroups. Deviating from the present assessment, the company nonetheless derived an indication of an added benefit of nivolumab in comparison with everolimus for the outcome "overall survival" for the total population.

Side effects

Discontinuation due to adverse events

There was an indication of an effect modification by the characteristic "number of antiangiogenic pretreatments" for the outcome "discontinuation due to AEs". A statistically significant effect in favour of nivolumab was shown for both patient groups with one or 2 pretreatments. Hence there was a hint of lesser harm from nivolumab in comparison with everolimus for the outcome "discontinuation" for patients with one or 2 antiangiogenic pretreatments.

Deviating from this, the company did not consider the effect modification because of results of the subgroup analyses that it considered to be homogeneous with those of the total population. For the total population, it derived an indication of lesser harm from nivolumab versus everolimus for the outcome.

Severe adverse events (CTCAE grade 3–4)

There was an indication of an effect modification by the characteristic "sex" for the outcome "severe AEs (CTCAE grade 3–4)". There was a statistically significant effect in favour of nivolumab for men. Hence there was a hint of lesser harm from nivolumab in comparison with everolimus for men. For women, however, there was no statistically significant difference between the treatment arms. Greater/lesser harm of nivolumab is therefore not proven for this patient group.

This assessment deviates from that of the company, which did not consider the effect modification because of results of the subgroup analyses that it considered to be homogeneous with those of the total population. It derived proof of lesser harm from nivolumab versus everolimus on the basis of the total population.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subpopulation 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 approach for deriving an overall conclusion on 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.

2.3.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.2 resulted in the following assessment of nivolumab in comparison with everolimus:

- an indication of an added benefit of nivolumab for patients with poor MSKCC score
- a hint of an added benefit of nivolumab for the outcomes "symptoms (FKSI-DRS)" and "health status (EQ-5D VAS)", in each case for the total population
- in each case a hint of lesser harm of nivolumab for the outcome "discontinuation due to AEs" for patients with one or 2 antiangiogenic pretreatments
- a hint of lesser harm of nivolumab for the outcome "severe AEs (CTCAE grade 3–4)"

Only qualitative consideration was possible of the results on specific AEs. Under certain conditions, conclusions could still be derived from the data, however (see Section 2.3.2.3 and Section 2.6.2.4.2 of the full dossier assessment). This interpretation resulted in a hint of lesser harm of nivolumab for the outcomes "pneumonitis", "mucosal inflammation", and "stomatitis", as well as an indication of lesser harm of nivolumab for the outcome "blood and lymphatic system disorders", in each case for the total population. In addition, greater harm of nivolumab regarding musculoskeletal pain (presented with the outcomes "arthralgia", "musculoskeletal pain", and "myalgia") could not be excluded.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 20).

Determination of the outcome category for the outcome "discontinuation due to AEs" and for specific AEs

The assessment of the outcome category for the outcomes "discontinuation due to AEs" and "specific AEs" depended on the severity of the AEs occurred.

In the CA209-025 study, the majority of discontinuations were due to severe AEs (CTCAE grade 3–4; nivolumab arm: 70%, everolimus arm: 62%). The results of the outcome "discontinuation due to AEs" were therefore allocated to the outcome category of serious/severe side effects.

Regarding specific AEs, the potentially important differences between the treatment arms occurred as non-serious and non-severe AEs for the following outcomes: infections and infestations, pneumonitis, mucosal inflammation, stomatitis, arthralgia, musculoskeletal pain, and myalgia. No potentially important differences between the treatment arms were determined under SAEs or severe AEs (CTCAE grade 3–4). The outcomes were therefore allocated to the category of non-serious/non-severe side effects.

Potentially important differences between the treatment arms on the basis of common severe AEs (CTCAE grade 3–4) were determined regarding the outcome "blood and lymphatic system disorders". This outcome was therefore allocated to the category of serious/severe side effects.

Table 20: 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 added benefit, extent: "non-quantifiable"[c]
Health status (EQ-5D VAS)	Mean change: 0.6 vs. -5.1 LSMD: 5.7 [3.8; 7.7] p < 0.001 Hedges' g: 0.44 [0.28; 0.59][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
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 20: 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 adverse events		
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[e]
Specific AEs (pneumonitis, mucosal inflammation, stomatitis)	Qualitative consideration probability: "hint"	Outcome category: non-serious/non-severe side effects lesser harm, extent: "non-quantifiable", "considerable"[f]
Specific AEs (arthralgia, musculoskeletal pain, myalgia)	Qualitative consideration	Outcome category: non-serious/non-severe side effects Greater harm not excluded[g]
Specific AEs (blood and lymphatic system disorders)	Qualitative consideration probability: "indication"	Outcome category: serious/severe side effects lesser harm, extent: "major"[h]

(continued)

Table 20: 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: Due to unclear patient inclusion in the analysis.
d: Added benefit assumed with upper and lower CI limits < –0.2 or > 0.2.
e: Results on the basis of the rates not statistically significantly different.
f: 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" ($CI_u < 0.80$).
g: Result on the basis of the rates with known direction of the bias to the disadvantage of nivolumab statistically significantly to the disadvantage of nivolumab.
h: 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 $\geq 5\%$).
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; LSMD: least-square mean difference; MSKCC: Memorial Sloan Kettering Cancer Center; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 21 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 21: 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: “non-quantifiable” ▪ health status (EQ-5D VAS): hint of an added benefit – extent: “non-quantifiable”	
Serious/severe side effects ▪ discontinuation due to adverse events ▫ 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 results showed a relevant effect modification by the MSKCC score for the outcome “overall survival”. Hereinafter, the overall conclusion on the added benefit for patients with poor MSKCC score and patients with favourable/intermediate MSKCC score is derived separately.

Furthermore, indications of an effect modification were shown for the outcome “discontinuation due to AEs” by the characteristic “number of antiangiogenic pretreatments”, and for the outcome “severe AEs (CTCAE grade 3–4)” by the characteristic “sex”. Since in both cases, these were only indications of an effect modification and no indication of an effect modification by both characteristics was identified for any other outcome, and in each case the effects were in the same direction, no differentiation by further characteristics besides the characteristic “MSKCC score” was conducted in the balancing of the added benefit.

Patients with poor MSKCC score

In the overall consideration, there were positive and negative effects for patients with poor MSKCC score. On the positive side, there was an indication of major added benefit of nivolumab for the outcome "overall survival" and hints of a non-quantifiable added benefit for the outcomes "symptoms (FKSI-DRS)" and "health status (EQ-5D VAS)". In addition, there were hints and indications of lesser harm of nivolumab with different extent in the category "side effects". On the negative side, greater harm from nivolumab concerning musculoskeletal pain could not be excluded.

Overall, the mortality advantage of nivolumab was supported by a consistent advantage in morbidity and side effects. The negative effects were so small that they did not raise doubts about the advantages of nivolumab, particularly those regarding overall survival.

In summary, there is an indication of a major added benefit of nivolumab in comparison with the ACT everolimus for the subgroup of patients with poor MSKCC score.

Patients with favourable/intermediate MSKCC score

For patients with favourable/intermediate MSKCC score, an added benefit for overall survival was not proven.

In addition, under consideration of the results that applied to the total population and therefore also to patients with favourable/intermediate MSKCC score, hints and indications of an added benefit or lesser harm of nivolumab with non-quantifiable to major extent remained in the outcome categories "morbidity" and "side effects", however. On the negative side, greater harm from nivolumab concerning musculoskeletal pain could not be excluded. Overall, the extent of added benefit of nivolumab was therefore assessed as considerable.

In summary, 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.

2.3.4 List of included studies

CA209-025

Bristol-Myers Squibb. Analyses of quality of life and resource utilization endpoints in a randomized, open-label, phase 3 study of Nivolumab (BMS-936558) versus Everolimus in subjects with advanced or metastatic clear-cell renal carcinoma (RCC): study CA209025; statistical analysis plan [unpublished].

Bristol-Myers Squibb. Core safety statistical analysis plan for multiple indications: Nivolumab program; statistical analysis plan [unpublished].

Bristol-Myers Squibb. Study of Nivolumab (BMS-936558) vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma (CheckMate 025): full text view [online]. In: CT.gov. [Accessed: 23.05.2016]. (Nct01668784). URL: https://ClinicalTrials.gov/show/NCT01668784.

Bristol-Myers Squibb Gmb H, Co K. Studienbericht der Studie CheckMate 025 (CA209-025).

Bristol-Myers Squibb International Corporation. A Randomized, Open-Label, Phase 3 Study of Nivolumab (BMS-936558) vs. Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Ther [online]. In: EU-CTR. [Accessed: 23.05.2016]. (2011-005132-26). URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005132-26.

Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. The New England Journal of Medicine 2015; 373(19): 1803-1813.

Ono Pharmaceutical. A Randomized, Open-Label, Phase 3 Study of ONO-4538/BMS-936558 vs. Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy [online]. In: JAPIC Clinical Trials Information. [Accessed: 23.05.2016]. (JPRN-JapicCTI-122014). URL: http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-122014.

Squibb B-M. Study of Nivolumab (BMS-936558) vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma (CheckMate 025): study results [online]. In: CT.gov. (Nct01668784). URL: https://clinicaltrials.gov/ct2/show/results/NCT01668784?show_locs=Y&sect=X4301256#othr.

2.4 Research question 2: adults with advanced renal cell carcinoma after prior therapy with temsirolimus

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on nivolumab (status: 30 March 2016)
- bibliographical literature search on nivolumab (last search on 10 March 2016)
- search in trial registries for studies on nivolumab (last search on 10 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 18 May 2016)

No additional relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified no studies investigating nivolumab in adults with advanced renal cell carcinoma after prior therapy with temsirolimus. Hence besides a direct comparison, also no indirect comparison of nivolumab and sunitinib with a common comparator is possible.

In summary, the company therefore presented no suitable studies to investigate the added benefit of nivolumab in comparison with the ACT for adults with advance renal cell carcinoma after prior therapy with temsirolimus.

2.4.2 Results on added benefit

No data were available for the assessment of the added benefit of nivolumab in the treatment of adults with advanced renal cell carcinoma after prior therapy with temsirolimus. Hence there was no hint of an added benefit of nivolumab in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of nivolumab in adults with advanced renal cell carcinoma after prior therapy with temsirolimus, an added benefit of nivolumab is not proven.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 22.

Table 22: Nivolumab – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Subgroup**	**Extent and probability of added benefit**
Adults with advanced renal cell carcinoma after prior therapy	Everolimus	Favourable/intermediate MSKCC score	Indication of considerable added benefit
		Poor MSKCC score	Indication of major added benefit
Adults with advanced renal cell carcinoma after prior therapy with temsirolimus	Sunitinib	Added benefit not proven	

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MSKCC: Memorial Sloan Kettering Cancer Center

This deviates from the company's approach, which derived proof of major added benefit for the total population of adults with advanced renal cell carcinoma after prior therapy. For adults with advanced renal cell carcinoma after prior therapy with temsirolimus, the company derived a hint of a non-quantifiable added benefit.

The approach for deriving an overall conclusion on 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.

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2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Bristol-Myers Squibb. OPDIVO 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 04.2016 [Accessed: 04.05.2016]. URL: http://www.fachinfo.de/.

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