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Nivolumab (renal cell carcinoma) –

Addendum to Commissions A19-11 and A19-12[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
SAE	serious adverse event
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 24 June 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for the commissions A19-11 (Nivolumab – Benefit assessment according to §35a Social Code Book V) [1] and A19-12 (Ipilimumab – Benefit assessment according to §35a Social Code Book V) [2].

In its comment from 5 June 2019 [3] and after the oral hearing, the pharmaceutical company (hereinafter referred to as "the company") presented further analyses on the CheckMate 214 study, which went beyond the information provided in the dossier [4,5].

The G-BA's commission comprised the following assessment:

- assessment of the event time analyses of severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4)
- assessment of the event time analyses of specific AEs subsequently submitted by the company with the comment
- assessment of the responder analyses on the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)

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

2 Assessment

The individual aspects commissioned by the G-BA are assessed below. They are divided as follows:

- Section 2.1 evaluates the methods of the data under assessment on event time analyses of severe AEs (CTCAE grade 3–4) and specific AEs, as well as of the responder analyses on the EQ-5D VAS.
- Sections 2.2 and 2.3 evaluate the results on the event time analyses of the severe AEs (CTCAE grade 3–4) and the specific AEs for patients with intermediate or poor-risk advanced renal cell carcinoma.

2.1 Evaluation of the methods of the data to be assessed in the addendum

2.1.1 Event time analyses of severe AEs (CTCAE grade 3–4)

For the severe AEs (CTCAE grade 3–4), the company presented time-to-first-event analyses in Module 4 of its dossier, indicating that the event with the highest severity grade was generally taken into account in the analysis for this outcome. As described in the dossier assessment [1,2], such an operationalization can lead to potentially biased results. For this reason, the dossier assessment used the relative risk as an effect measure for the assessment of severe AEs (CTCAE grade 3–4).

The company explained in its comment that, in each case, the time to first grade 3 or 4 AE was considered in the event time analyses presented in Module 4. Such an operationalization of severe AEs (CTCAE grade 3–4) is adequate and is used for the benefit assessment.

Risk of bias of the results on severe AEs (CTCAE grade 3–4)

As described in the dossier assessment [1,2], the risk of bias of the results for the outcome "severe AEs (CTCAE grade 3–4)" is rated as high due to potentially informative censoring. At most hints of greater or lesser harm can therefore be derived.

2.1.2 Event time analyses of specific adverse events

In its dossier, the company presented results on proportions of patients with AEs at System Organ Class (SOC) and Preferred Term (PT) level for common AEs, serious AEs (SAEs), severe AEs (CTCAE grade 3–4) and discontinuations due to AEs for research question 1 (patients with intermediate risk) and 2 (patients with poor risk). The dossier assessment [1,2] used specific AEs based on relative risks calculated by the Institute.

In its written comments and after the oral hearing, the company subsequently submitted event time analyses on the individual common AEs, SAEs and severe AEs (CTCAE grade 3–4).

As described in the dossier assessment [1,2], there were differences between both study arms in the CheckMate 214 study in the median treatment and observation periods in both sub-populations considered. Taking into account the size of the differences in the observation periods, analyses of relative risks provide interpretable results. Event time analyses are a more suitable method of analysis for the assessment of side effects in this situation, however, and are therefore used for the benefit assessment.

Risk of bias of the results on specific adverse events

As described in the dossier assessment [1,2], the risk of bias of the results on specific AEs was rated as high due to potentially informative censoring and lack of blinding in subjective recording of outcomes (only for non-serious/non-severe AEs). At most hints of greater or lesser harm can therefore be derived.

2.1.3 Responder analyses of EQ-5D VAS

As already described in the dossier assessment [1,2], the responder analyses on the deterioration by at least 7 or 10 points presented by the company for the outcome “health status” (recorded with the EQ-5D VAS) are unsuitable for the benefit assessment. The analysis of the mean change is the relevant analysis for the assessment. The responder analyses on the EQ-5D VAS for time to confirmed deterioration is presented as additional information in Appendix B.

2.2 Research question 1: patients with intermediate risk

2.2.1 Results

Severe adverse events (CTCAE grade 3–4)

Table 1 shows the results on the time to first event of severe AEs (CTCAE grade 3–4) in patients with intermediate risk.

Table 1: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (patients with intermediate risk) Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (patients with intermediate risk)

Study Outcome category Outcome	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median time to event in months [95% CI] Patients with event n (%)	Sunitinib N	Sunitinib Median time to event in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. sunitinib HR [95% CI]; p-value[a]
CheckMate 214					
Side effects					
Severe AEs (CTCAE grade 3–4)[b]	333	4.21 [3.06; 5.32] 244 (73.3)	329	2.14 [1.91; 2.86] 260 (79.0)	0.66 [0.55; 0.79]; < 0.001

a: HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by IMDC score (1–2, 3–6) and region (USA, Canada/Western Europe/Northern Europe, rest of the world) according to IVRS.
b: 100-day follow-up without recording of progression of the underlying disease.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IVRS: interactive voice response system; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

A statistically significant difference between the treatment arms in favour of nivolumab + ipilimumab was shown for the outcome "severe AEs (CTCAE grade 3–4)" in patients with intermediate risk. This resulted in a hint of lesser harm of nivolumab + ipilimumab in comparison with sunitinib for this outcome.

The analysis of the time to first event of severe AEs (CTCAE grade 3–4) in comparison with the relative risk used in dossier assessments A19-11 and A19-12 [1,2] resulted in an additional advantage of nivolumab + ipilimumab.

Specific adverse events

Table 2 shows results on specific AEs chosen on the basis of the event time analyses subsequently submitted for patients with intermediate risk chosen. In cases in which the hazard ratio from survival time analyses was not calculable due to 0 events in a study arm, relative risks were still presented and used to determine the added benefit.

Table 2: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (patients with intermediate risk)

Study Outcome category Outcome	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value
Side effects					
Specific adverse events					
Mucosal inflammation (PT, severe AE [CTCAE grade 3–4])	333	ND 1 (0.3)	329	ND 10 (3.0)	0.10 [0.01; 0.74]; ND
Malaise (PT, AE)	333	ND 8 (2.4)	329	ND 21 (6.4)	0.36 [0.16; 0.81]; ND
Oedema (PT, AE)	333	ND 4 (1.2)	329	ND 18 (5.5)	0.21 [0.07; 0.63]; ND
Gastrointestinal disorders (SOC, AE)	333	ND 238 (71.5)	329	ND 287 (87.2)	0.46 [0.39; 0.55]; ND
Diarrhoea (PT, SAE)	333	ND 11 (3.3)	329	ND 2 (0.6)	5.53 [1.23; 24.97]; ND
Pruritus (PT, AE)	333	ND 126 (37.8)	329	ND 38 (11.6)	3.85 [2.68; 5.54]; ND
Rash (PT, AE)[b]	333	ND 88 (26.4)	329	ND 57 (17.3)	1.57 [1.12; 2.20]; ND
Palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])	333	ND 1 (0.3)	329	ND 25 (7.6)	0.04 [0.01; 0.28]; ND
Hair colour changes (PT, AE)	333	ND 0 (0)	329	ND 19 (5.8)	RR: 0.03 [0.00; 0.42]; < 0.001[c]
Yellow skin (PT, AE)[d]	333	ND 0 (0)	329	ND 31 (9.4)	RR: 0.02 [0.00; 0.26]; < 0.001[c]
Myalgia (PT, AE)	333	ND 51 (15.3)	329	ND 23 (7.0)	2.27 [1.39; 3.72]; ND
Influenza (PT, AE)	333	ND 17 (5.1)		ND 5 (1.5)	3.14 [1.15; 8.52]; ND
Pneumonia (PT, severe AE [CTCAE grade 3–4])	333	ND 10 (3.0)	329	ND 2 (0.6)	4.96 [1.09; 22.64]; ND

(continued)

Table 2: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (patients with intermediate risk) (continued)

Study Outcome category Outcome	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value
Pneumonitis (PT, SAE)	333	ND 11 (3.3)	329	ND 0 (0)	RR: 22.72 [1.34; 384.05]; < 0.001[c]
Epistaxis (PT, AE)	333	ND 5 (1.5)	329	ND 46 (14.0)	0.09 [0.03; 0.22]; ND
Hyperglycaemia (PT, severe AE [CTCAE grade 3–4])	333	ND 14 (4.2)	329	ND 3 (0.9)	4.31 [1.23; 15.08]; ND
Decreased appetite (PT, AE)	333	ND 66 (19.8)	329	ND 95 (28.9)	0.62 [0.45; 0.85]; ND
Dysgeusia (PT, AE)	333	ND 22 (6.6)	329	ND 109 (33.1)	0.16 [0.10; 0.25]; ND
Endocrine disorders (SOC, severe AE [CTCAE grade 3–4])	333	ND 22 (6.6)	329	ND 1 (0.3)	2.62 [3.05; > 99.99]; ND
Hypertension (PT, severe AE [CTCAE grade 3–4])	333	ND 9 (2.7)	329	ND 58 (17.6)	0.13 [0.07; 0.27] ND
Blood and lymphatic system disorders (SOC, severe AE [CTCAE grade 3–4])	333	ND 14 (4.2)	329	ND 44 (13.4)	0.30 [0.17; 0.55]; ND
Vision blurred (PT, AE)	333	ND 19 (5.7)	329	ND 5 (1.5)	3.61 [1.35; 9.69]; ND

a: HR and CI: Cox proportional hazards model; stratified by IMDC score (1–2, 3–6) and region (USA, Canada/Western Europe/Northern Europe, rest of the world) according to IVRS.
b: There is a significant difference between the treatment groups to the disadvantage of nivolumab + ipilimumab for the PT "rash maculo-papular" (AE).
c: In case of 0 events, the HR was not calculable, and the Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]) was used; the correction factor of 0.5 was used in the calculation in both study arms.
d: There is a significant difference between the treatment groups in favour of nivolumab + ipilimumab for the PT "skin discolouration" (AE).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IVRS: interactive voice response system; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The consideration of the event time analyses produced no important differences in the choice of specific AEs. In contrast to the consideration of relative risks, based on event time analyses,

the AEs “influenza like illness” (PT, AE) and “arthralgia” (PT, AE) were not chosen as specific AEs (for comparison, see [1,2]). The AEs “influenza” (PT, AE), “decreased appetite” (PT, AE) and “vision blurred” (PT, AE), however, were included in the selection as specific AEs.

The data on AEs assessed in the present addendum showed both advantages and disadvantages of nivolumab + ipilimumab in comparison with sunitinib.

There were statistically significant differences between the treatment arms in favour of nivolumab + ipilimumab in comparison with sunitinib in the following AEs:

- severe AEs (CTCAE grade 3–4)
- specific AEs (AEs, SAEs, severe AEs [CTCAE grade 3–4]):
  - mucosal inflammation (PT, severe AE [CTCAE grade 3–4])
  - malaise (PT, AE)
  - oedema (PT, AE)
  - gastrointestinal disorders (SOC, AE)
  - palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])
  - hair colour changes (PT, AE)
  - yellow skin (PT, AE)
  - epistaxis (PT, AE)
  - decreased appetite (PT, AE)
  - dysgeusia (PT, AE)
  - hypertension (PT, severe AE [CTCAE grade 3–4])
  - blood and lymphatic system disorders (SOC, severe AE [CTCAE grade 3–4])

Significant differences between the treatment arms to the disadvantage of nivolumab + ipilimumab in comparison with sunitinib were shown for the following AEs:

- specific AEs (AEs, SAEs, severe AEs [CTCAE grade 3–4])
  - diarrhoea (PT, SAE)
  - pruritus (PT, AE)
  - rash (PT, AE)
  - myalgia (PT, AE)
  - influenza (PT, AE)
  - pneumonia (PT, severe AE [CTCAE grade 3–4])
  - pneumonitis (PT, SAE)

- hyperglycaemia (PT, severe AE [CTCAE grade 3–4])
- endocrine disorders (SOC, severe AE [CTCAE grade 3–4])
- vision blurred (PT, AE)

As described in the dossier assessment [1,2], disadvantages of nivolumab + ipilimumab in comparison with sunitinib were also shown for

- SAEs and
- discontinuation due to AEs.

Overall, there were still hints both of lesser and of greater harm from nivolumab + ipilimumab in comparison with sunitinib with the extents "minor" to "major". Indications of lesser or greater harm were derived for individual specific AEs (see dossier assessment for reasons [1,2]).

Table 3 and Table 9 in Appendix A show the probability and extent of the added benefit for the side effect outcomes for patients with intermediate-risk advanced renal cell carcinoma under consideration of dossier assessments A19-11 and A19-12 and the present addendum.

There are only few changes in the results on specific AEs in comparison with the dossier assessment:

- there are 1 additional positive (decreased appetite [PT]) and 2 additional negative effects (influenza and vision blurred [each PT]) for non-serious/non-severe AEs
- 2 negative effects in non-serious/non-severe AEs are no longer present (influenza like illness and arthralgia [each PT])

The direction of effect did not change in any of the chosen specific AEs, and the extent of the added benefit changed in only few specific AEs. The individual changes in the extent of the effect in comparison with the dossier assessment are indicated in Table 9.

On the whole, the advantages and disadvantages of nivolumab + ipilimumab in comparison with sunitinib regarding side effects are balanced in patients with intermediate risk, also under consideration of the analyses subsequently submitted. Overall, this resulted in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with sunitinib for side effects; greater or lesser harm is therefore not proven. This concurs with the assessment in the dossier assessment [1,2].

Subgroups and other effect modifiers

In accordance with the methods described in the dossier assessment [1,2], no effect modification by the relevant subgroup characteristics was shown for the outcome "severe AEs (CTCAE grade 3–4)". There are not subgroup analyses for the specific AEs.

2.2.2 Extent and probability of added benefit (research question 1)

Table 3 and Table 9 show the probability and extent of the added benefit for severe AEs and specific AEs for patients with intermediate-risk advanced renal cell carcinoma.

Table 3: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (patients with intermediate prognosis)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or mean value or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	Median: 9.1 vs. 20.8 months HR: 1.38 [1.11; 1.71] HR: 0.73 [0.58; 0.90][d] p = 0.004 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Severe AEs (CTCAE grade 3–4)	Median: 4.21 vs. 2.14 HR: 0.66 [0.55; 0.79]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: “considerable”
Discontinuation due to AEs	Median: NA vs. NA HR: 1.51 [1.09; 2.09] HR: 0.66 [0.48; 0.92][d] p = 0.012 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Specific adverse events		
▪ Malaise ▪ Decreased appetite	-[e]	Lesser harm, extent: “minor”
▪ Gastrointestinal disorders ▪ Mucosal inflammation ▪ Hair colour changes ▪ Yellow skin ▪ Oedema ▪ Epistaxis ▪ Dysgeusia	-[e]	Lesser harm, extent: “considerable”
▪ Palmar-plantar erythrodysaesthesia syndrome ▪ Hypertension ▪ Blood and lymphatic system disorders	-[e]	lesser harm, extent: “major”

(continued)

Table 3: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (patients with intermediate prognosis) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or mean value or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
▪ Influenza ▪ Rash ▪ Pneumonia	-[e]	Greater harm, extent: “minor”
▪ Diarrhoea ▪ Pruritus ▪ Myalgia ▪ Vision blurred ▪ Hyperglycaemia	-[e]	Greater harm, extent: “considerable”
▪ Endocrine disorders ▪ Pneumonitis	-[e]	Greater harm, extent: “major”

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval CI_u.
c: If the CI of Hedges’ g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d: Institute’s calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: See Table 9 for a detailed presentation.
AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; HR: hazard ratio; CTCAE: Common Terminology Criteria for Adverse Events; NA: not achieved; SAE: serious adverse event; vs.: versus

Summary

In summary, there is an additional advantage regarding severe AEs (CTCAE grade 3–4) for patients with intermediate risk in comparison with the dossier assessment. Furthermore, the survival time analyses subsequently submitted produced only few changes in the assessment of the results on specific AEs in comparison with the dossier assessment. The results were largely based on the same events. In no case did the direction of the effect of the chosen specific AEs change, and the extent of the added benefit also only changed in some specific AEs. Overall, this resulted in no changes in the conclusion on side effects and hence in no change in the overall conclusion on the added benefit of nivolumab + ipilimumab in comparison with the appropriate comparator therapy.

2.3 Research question 2: patients with poor risk

2.3.1 Results

Severe AEs (CTCAE grade 3–4)

Table 4 shows the results on the time to first event of severe AEs (CTCAE grade 3–4) in patients with poor risk.

Table 4: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (patients with poor risk)

Study Outcome category Outcome	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
CheckMate 214					
Side effects					
Severe AEs (CTCAE grade 3–4)[b]	90	2.76 [1.58; 4.86] 71 (78.9)	87	1.35 [0.85; 2.10] 76 (87.4)	0.57 [0.41; 0.81]; 0.001

a: HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by IMDC score (1–2, 3–6) and region (USA, Canada/Western Europe/Northern Europe, rest of the world) according to IVRS.
b: 100-day follow-up without recording of progression of the underlying disease.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IVRS: interactive voice response system; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

A statistically significant difference in favour of nivolumab + ipilimumab was shown for the outcome "severe AEs (CTCAE grade 3–4)" in patients with poor risk. An effect modification by the characteristic "age" was additionally shown (see below). This resulted in a hint of lesser harm of nivolumab + ipilimumab in comparison with sunitinib for patients aged 65 years and older. For patients under 65 years of age, there was no hint of greater or lesser harm of nivolumab + ipilimumab; greater or lesser harm for these patients is therefore not proven.

The analysis of the time to first event of severe AEs (CTCAE grade 3–4) in comparison with the relative risk used in dossier assessments A19-11 and A19-12 [1,2] showed an additional advantage of nivolumab + ipilimumab in patients aged 65 years and older.

Specific adverse events

Table 5 shows results on specific AEs chosen on the basis of the event time analyses subsequently submitted. In cases in which the hazard ratio from survival time analyses was not

calculable due to 0 events in a study arm, relative risks were still presented and used to determine the added benefit.

Table 5: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (patients with poor risk)

Study Outcome category Outcome	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value
Side effects					
Specific AEs					
Stomatitis (PT, AE)	90	ND 2 (2.2)	87	ND 15 (17.2)	0.12 [0.03; 0.51]; ND
Fever (PT, AE)	90	ND 26 (28.9)	87	ND 9 (10.3)	2.71 [1.26; 5.80]; ND
Mucosal inflammation (PT, AE)	90	ND 1 (1.1)	87	ND 25 (28.7)	0.03 [0.00; 0.21]; ND
Epistaxis (PT, AE)	90	ND 1 (1.1)	87	ND 9 (10.3)	0.09 [0.01; 0.74]; ND
Pruritus (PT, AE)	90	ND 22 (24.4)	87	ND 7 (8.0)	2.94 [1.25; 6.95]; ND
Palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])	90	ND 0 (0)	87	ND 7 (8.0)	RR: –[b]; 0.007[c]
Dysgeusia (PT, AE)	90	ND 7 (7.8)	87	ND 24 (27.6)	0.22 [0.09; 0.51]; ND
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	90	ND 8 (8.9)	87	ND 17 (19.5)	0.34 [0.15; 0.82]; ND
Hypothyroidism (PT, AE)	90	ND 5 (5.6)	87	ND 16 (18.4)	0.23 [0.08; 0.63]; ND
Gastrointestinal disorders (SOC, severe AE [CTCAE grade 3–4])	90	ND 7 (7.8)	87	ND 17 (19.5)	0.38 [0.16; 0.92]; ND
Thrombocytopenia (PT, severe AE [CTCAE grade 3–4])	90	ND 0 (0)	87	ND 7 (8.0)	RR: –[b]; 0.007[c]
Hypertension (PT, severe AE [CTCAE grade 3–4])	90	ND 4 (4.4)	87	ND 11 (12.6)	0.20 [0.05; 0.71]; ND

(continued)

Table 5: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (patients with poor risk) (continued)

a: HR and CI: Cox proportional hazards model; stratified by IMDC score (1–2, 3–6) and region (USA, Canada/Western Europe/Northern Europe, rest of the world) according to IVRS.
b: No presentation of effect estimation and CI as these are not informative.
c: In case of 0 events, the HR was not calculable, and the Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]) was used; the correction factor of 0.5 was used in the calculation in both study arms.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; ND: no data; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IVRS: interactive voice response system; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The consideration of the event time analyses produced no important differences in the choice of specific AEs. In contrast to the consideration of relative risks, based on event time analyses, the AE "ear and labyrinth disorders" (SOC, AE) was not chosen as specific AE (for comparison, see [1,2]). In contrast, the AE "hypertension" (PT, severe AE [CTCAE grade 3–4]) was chosen as specific AE based on event time analyses (for comparison, see [1,2]).

Statistically significant differences in favour of nivolumab + ipilimumab in comparison with sunitinib were shown for the following outcomes: stomatitis, mucosal inflammation, epistaxis, palmar-plantar erythrodysaesthesia syndrome, dysgeusia, respiratory, thoracic and mediastinal disorders, hypothyroidism, gastrointestinal disorders, thrombocytopenia, and hypertension. Under consideration of the risk of bias, this resulted in each case in a hint of lesser harm of nivolumab + ipilimumab in comparison with sunitinib.

There were statistically significant differences to the disadvantage of nivolumab + ipilimumab in comparison with sunitinib for the outcomes "fever" and "pruritus". Under consideration of the risk of bias, this resulted in each case in a hint of greater harm of nivolumab + ipilimumab in comparison with sunitinib.

There are only few changes in the results on specific AEs in comparison with the dossier assessment:

- there is 1 additional positive effect for severe AEs (hypertension [PT])
- 1 negative effect in non-serious/non-severe AEs is no longer present (ear and labyrinth disorders [SOC])

The direction of effect did not change in any of the chosen specific AEs, and the extent of the added benefit changed in only few specific AEs. The individual changes in the extent of the effect in comparison with the dossier assessment are indicated in Table 7.

Subgroups and other effect modifiers

The methods for the consideration of subgroups and other effect modifiers as well as the relevant subgroup characteristics considered are described in the dossier assessment [1,2].

Table 6 shows the results of the subgroup analyses for the outcome "severe AEs" (CTCAE grade 3–4) in patients with poor risk. There are not subgroup analyses for the specific AEs.

Table 6: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (patients with poor prognosis)

Study Outcome Characteristic Subgroup	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median time to event in months [95% CI] Patients with event n (%)	Sunitinib N	Sunitinib Median time to event in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. sunitinib HR [95% CI]; p-value[a]
CheckMate 214					
Severe AEs (CTCAE grade 3–4)[b]					
Age category III					
< 65 years	58	2.33 [1.38; 3.88] 48 (82.8)	53	1.77 [1.18; 2.79] 46 (86.8)	0.70 [0.46; 1.07]; 0.094
≥ 65 years to < 75 years	24	5.13 [0.82; 12.62] 17 (70.8)	27	0.99 [0.69; 3.81] 23 (85.2)	0.47 [0.24; 0.92]; 0.024
≥ 75 years	8	2.71 [0.16; NC] 6 (75.0)	7	0.49 [0.13; 0.72] 7 (100.0)	0.06 [0.01; 0.54]; 0.002
Total					Interaction[c]: 0.022

a: HR and CI: unstratified Cox proportional hazards model, p-value: unstratified log-rank test.
b: 100-day follow-up without recording of progression of the underlying disease.
c: Interaction test from Cox proportional hazards model adjusted by treatment and age categories, as well as an interaction term between treatment and age categories.
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; NC: not calculable; RCT: randomized controlled trial; vs.: versus

For the outcome "severe AEs" (CTCAE grade 3–4), there was an effect modification by the characteristic "age" (< 65 years/≥ 65 years to < 75 years/≥ 75 years) for patients with poor prognosis.

For patients aged < 65 years, there was no statistically significant difference between the treatment groups for the outcome "severe AEs". This resulted in no hint of greater or lesser harm of nivolumab + ipilimumab for patients aged < 65 years; greater or lesser harm for these patients is therefore not proven.

There was a statistically significant difference in favour of nivolumab + ipilimumab for patients aged ≥ 65 years to < 75 years and aged ≥ 75 years. This resulted in a hint of lesser harm from nivolumab + ipilimumab in comparison with sunitinib in each case.

2.3.2 Extent and probability of added benefit (research question 2)

Table 7 shows the probability and extent of the added benefit for severe AEs and specific AEs for patients with poor-risk advanced renal cell carcinoma. The individual changes in the extent of the effect in comparison with the dossier assessment are indicated in Table 7.

Table 7: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (patients with poor risk)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
Severe AEs (CTCAE grade 3–4)		
Age		
< 65 years	Median: 2.33 vs. 1.77 HR: 0.70 [0.46; 1.07]; p = 0.094	Greater/lesser harm not proven
≥ 65 years to < 75 years	Median: 5.13 vs. 0.99 0.47 [0.24; 0.92]; p = 0.024 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.0$ lesser harm, extent: “minor”
≥ 75 years	Median: 2.71 vs. 0.49 0.06 [0.01; 0.54]; p = 0.002 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: “major”

(continued)

Table 7: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (patients with poor risk) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Specific AEs		
Stomatitis (PT, AE)	Median: ND HR: 0.12 [0.03; 0.51]; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Fever (PT, AE)	Median: ND HR: 2.71 [1.26; 5.80] HR: 0.37 [0.17; 0.79]c; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Mucosal inflammation (PT, AE)	Median: ND HR: 0.03 [0.00; 0.21]; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Epistaxis (PT, AE)	Median: ND HR: 0.09 [0.01; 0.74]; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"[d]
Pruritus (PT, AE)	Median: ND HR: 2.94 [1.25; 6.95] HR: 0.34 [0.14; 0.80][c]; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"[e]
Palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])	0.0% vs. 8% RR –[f] p = 0.007 probability: "hint"	Outcome category: non-serious/non-severe side effects lesser harm, extent: "non-quantifiable"
Dysgeusia (PT, AE)	Median: ND HR: 0.22 [0.09; 0.51]; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	Median: ND HR: 0.34 [0.15; 0.82]; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"[d]

(continued)

Table 7: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (patients with poor risk) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Hypothyroidism (PT, AE)	Median: ND HR: 0.23 [0.08; 0.63]; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Gastrointestinal disorders (SOC, severe AE [CTCAE grade 3–4])	Median: ND HR: 0.38 [0.16; 0.92]; p = ND probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.0$ lesser harm, extent: "minor"
Thrombocytopenia (PT, severe AE [CTCAE grade 3–4])	0% vs. 8% RR: –[f] p = 0.007 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Hypertension (PT, severe AE [CTCAE grade 3–4])	Median: ND HR: 0.20 [0.05; 0.71]; p = ND probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval CI_u.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: The consideration of relative risks results in an effect with the extent "minor".
e: The consideration of relative risks results in an effect with the extent "considerable".
f: No presentation of effect estimation and CI as these are not informative.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ND: no data; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Summary

In summary, there is an additional advantage regarding severe AEs (CTCAE grade 3–4) for patients with poor risk aged 65 years and older in comparison with the dossier assessment. Furthermore, the survival time analyses subsequently submitted produced only few changes in the assessment of the results on specific AEs in comparison with the dossier assessment. The results were largely based on the same events. In no case did the direction of the effect of the chosen specific AEs change, and the extent of the added benefit also only changed in some specific AEs. Overall, this resulted in no changes in the overall conclusion on the added benefit of nivolumab + ipilimumab in comparison with the appropriate comparator therapy.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure and presented in the present addendum do not change the conclusion on the added benefit of nivolumab + ipilimumab (or ipilimumab + nivolumab) for patients with advanced renal cell carcinoma from the dossier assessments A19-11 and A19-12.

The following Table 8 shows the result of the benefit assessment of nivolumab + ipilimumab under consideration of the dossier assessments A19-11 and A19-12 and the present addendum.

Table 8: Nivolumab + ipilimumab – probability and extent of added benefit

Research question	**Subindication**	**ACT**[a]	**Probability and extent of added benefit**
1	Treatment-naive adult patients with intermediate-risk advanced renal cell carcinoma (1−2 risk factors as per the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or **sunitinib**	Indication of considerable added benefit[b]
2	Treatment-naive adult patients with poor-risk advanced renal cell carcinoma (≥ 3 risk factors as per the IMDC criteria)	Temsirolimus or **sunitinib**	Indication of a major added benefit[b]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The CheckMate 214 study underlying the benefit assessment did not investigate patients with non-clear cell renal cell carcinoma, advanced AJCC stage III renal cell carcinoma, brain metastases, or Karnofsky performance status < 70% (see dossier assessment [1,2]). It is unclear whether the observed effects are transferable to patients with the characteristics described above.
ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; G-BA: Federal Joint Committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

The G-BA decides on the added benefit.

3 References

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Appendix A – Results on side effects (research question 1: patients with intermediate risk)

Table 9: Extent of added benefit at outcome level for specific AEs: nivolumab + ipilimumab vs. sunitinib (patients with intermediate risk)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months)** **or** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
Specific AEs		
Mucosal inflammation (PT, severe AE [CTCAE grade 3–4])	Median: ND HR: 0.10 [0.01; 0.74]; p = ND probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk < 5% lesser harm, extent: "considerable"
Malaise (PT, AE)	Median: ND HR: 0.36 [0.16; 0.81]; p = ND probability: "hint"	Outcome category: non-serious/ non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Oedema (PT, AE)	Median: ND HR: 0.21 [0.07; 0.63]; p = ND probability: "hint"	Outcome category: non-serious/ non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Gastrointestinal disorders (SOC, AE)	Median: ND HR: 0.46 [0.39; 0.55]; p = ND probability: "hint"	Outcome category: non-serious/ non-severe side effects lesser harm, extent: "considerable"[c]
Diarrhoea (PT, SAE)	Median: ND HR: 5.53 [1.23; 24.97] HR: 0.18 [0.04; 0.81][d]; p = ND probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Pruritus (PT, AE)	Median: ND HR: 3.85 [2.68; 5.54] HR: 0.26 [0.18; 0.37][d]; p = ND probability: "hint"	Outcome category: non-serious/ non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

(continued)

Table 9: Extent of added benefit at outcome level for specific AEs: nivolumab + ipilimumab vs. sunitinib (patients with intermediate risk) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Rash (PT, AE)	Median: ND HR: 1.57 [1.12; 2.20] HR: 0.64 [0.45; 0.89][d]; p = ND probability: “hint”	Outcome category: non-serious/ non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: “minor”
Palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])	Median: ND HR: 0.04 [0.01; 0.28]; p = ND probability: “indication”[e]	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: “major”
Hair colour changes (PT, AE)	0% vs. 5.8% RR: 0.03 [0.00; 0.42][f]; p < 0.001 probability: “hint”	Outcome category: non-serious/ non-severe side effects $CI_u < 0.80$ lesser harm, extent: “considerable”
Yellow skin (PT, AE)	0% vs. 9.4% RR: 0.02 [0.00; 0.26][f]; p < 0.001 probability: “hint”	Outcome category: non-serious/ non-severe side effects $CI_u < 0.80$ lesser harm, extent: “considerable”
Myalgia (PT, AE)	Median: ND HR: 2.27 [1.39; 3.72] HR: 0.44 [0.27; 0.72][d]; p = ND probability: “hint”	Outcome category: non-serious/ non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Influenza (PT, AE)	Median: ND HR: 3.14 [1.15; 8.52] HR: 0.32 [0.12; 0.87][d]; p = ND probability: “hint”	Outcome category: non-serious/ non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: “minor”
Pneumonia (PT, severe AE [CTCAE grade 3–4])	Median: ND HR: 4.96 [1.09; 22.64] HR: 0.20 [0.04; 0.92][d]; p = ND probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”

(continued)

Table 9: Extent of added benefit at outcome level for specific AEs: nivolumab + ipilimumab vs. sunitinib (patients with intermediate risk) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Pneumonitis (PT, SAE)	3.3% vs. 0% RR: 22.72 [1.34; 384.05][f] RR: 0.04 [0.00; 0.746][d]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ greater harm, extent: "major"
Epistaxis (PT, AE)	Median: ND HR: 0.09 [0.03; 0.22]; p = ND probability: "hint"	Outcome category: non-serious/ non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Hyperglycaemia (PT, severe AE [CTCAE grade 3–4])	Median: ND HR: 4.31 [1.23; 15.08] HR: 0.23 [0.07; 0.81][d]; p = ND probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent "considerable"[g]
Decreased appetite (PT, AE)	Median: ND HR: 0.62 [0.45; 0.85]; p = ND probability: "hint"	Outcome category: non-serious/ non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Dysgeusia (PT, AE)	Median: ND HR: 0.16 [0.10; 0.25]; p = ND probability: "hint"	Outcome category: non-serious/ non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Endocrine disorders (SOC, severe AE [CTCAE grade 3–4])	Median: ND HR: 2.62 [3.05; > 99.99] HR: 0.38 [< 0.01; 0.33][c]; p = ND probability: "indication"[e]	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent "major"

(continued)

Table 9: Extent of added benefit at outcome level for specific AEs: nivolumab + ipilimumab vs. sunitinib (patients with intermediate risk) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Hypertension (PT, severe AE [CTCAE grade 3–4])	Median: ND HR: 0.13 [0.07; 0.27]; p = ND probability: "indication"[d]	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"
Blood and lymphatic system disorders (SOC, severe AE [CTCAE grade 3–4])	Median: ND HR: 0.30 [0.17; 0.55]; p = ND probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"
Vision blurred (PT, AE)	Median: ND HR: 3.61 [1.35; 9.69] HR: 0.28 [0.10; 0.74][c]; p = ND probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval CI_u.
c: The consideration of relative risks results in an effect with the extent "minor".
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: The certainty of results is considered high because the observation of such a large effect is not explicable solely by potentially informative reasons for discontinuation.
f: In case of 0 events, the HR was not calculable, and the Institute performed its calculation of RR and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]); the correction factor of 0.5 was used in the calculation in both study arms.
g: The consideration of relative risks results in an effect with the extent "major".

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ND: no data; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Appendix B – Supplementary presentation of the responder analyses of the EQ-5D VAS

Table 10: Results (health status) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with intermediate risk)

Study Outcome category Outcome	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median time to event in months [95% CI] Patients with event n (%)	Sunitinib N	Sunitinib Median time to event in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. sunitinib HR [95% CI]; p-value[a]
CheckMate 214					
Morbidity					
EQ-5D VAS (time to confirmed deterioration[b])					
MID 7 points (additional information)	334	28.58 [26.32; NA] 120 (35.9)	333	25.59 [20.96; 27.83] 132 (39.6)	0.78 [0.61; 1.01]; 0.057
MID 10 points (additional information)	334	29.96 [26.51; NA] 116 (34.7)	333	26.25 [23.95; 28.03] 126 (37.8)	0.80 [0.62; 1.03]; 0.086

a: HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by IMDC score (1–2, 3–6) and region (USA, Canada/Western Europe/Northern Europe, rest of the world) according to IVRS and adjusted by baseline value.

b: It is rated as confirmed deterioration if a deterioration of the values by at least 7 or 10 points remains or if no data are available after deterioration. Patients with improvement of values to a range that is not clinically relevant are censored. All recorded time points including the follow-up time points are included in the analysis.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IVRS: interactive voice response system; MID: minimally important difference; n: number of patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Table 11: Results (health status) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with poor risk)

Study **Outcome category**	**Nivolumab + ipilimumab**		**Sunitinib**		**Nivolumab + ipilimumab vs. sunitinib**
Outcome	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
CheckMate 214					
Morbidity					
EQ-5D VAS (time to confirmed deterioration[b])					
MID 7 points (additional information)	91	26.32 [21.42; NA] 29 (31.9)	89	21.91 [15.05; NA] 23 (25.8)	0.64 [0.36; 1.13]; 0.122
MID 10 points (additional information)	91	26.32 [21.42; NA] 29 (31.9)	89	21.91 [15.05; NA] 22 (24.7)	0.67 [0.38; 1.21]; 0.184

a: HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by IMDC score (1–2, 3–6) and region (USA, Canada/Western Europe/Northern Europe, rest of the world) according to IVRS and adjusted by baseline value.

b: It is rated as confirmed deterioration if a deterioration of the values by at least 7 or 10 points remains or if no data are available after deterioration. Patients with improvement of values to a range that is not clinically relevant are censored. All recorded time points including the follow-up time points are included in the analysis.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IVRS: interactive voice response system; MID: minimally important difference; n: number of patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus